British Journal of Plastic Surgery (1992), 45, 315–321

BRITISH JOURNAL OF PLASTIC SURGERY

Breast implant materials: sense and safety

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SUMMARY. **Cosmetic breast augmentation, and post-mastectomy breast reconstruction surgery using synthetic implants, have become established in surgical practice over more than 20 years. The operative techniques for implant placement have changed somewhat during this time, as many different implant presentations have become available, but the same basic materials have remained in use.**

We have reviewed the present state of knowledge about breast implant materials with particular reference to the possible connection between polydimethylsiloxane and polyurethane to the so-called "Human Adjuvant Disease", and to carcinogenesis. Problems related to capsular contracture and mammography are also discussed.

The psychological benefits afforded by breast reconstruction or in primary augmentation are well recognised (Shipley *et al.*, 1977; Beale *et al.*, 1984). However the safety of the materials used in breast augmentation has been called into question and a review of these concerns is now timely.

Silicones

Physical form

Mammary implants contain silicone materials in the following forms:

1. *Silicone fluid* (polydimethylsiloxane, PDMS). This is the fluid component of silicone gel, and it is this which may "bleed" through the elastomer envelope of the prosthesis.
2. *Silicone gel* is the "thick" form in which gel is provided to fill the implant envelope.
3. *Silicone Elastomer* forms the envelope within which the fluid and gel are contained. "High Performance" elastomers have a high tear resistance, and other materials may be added (*e.g.* barium sulphate to impart radio-opacity).

Tissue reactivity

Silicone fluid, or polydimethylsiloxane (PDMS), was itself originally injected directly into tissue as an augmentation material and was believed to excite a minimal cellular reaction. More recent studies have suggested that the intensity of the cellular reaction increases as molecular weight increases. The tissue reaction is least to silicone fluid and maximum to fumed silica, which is present in the envelope of implants (Picha and Goldstein, 1991).

PDMS has an average molecular weight of 24000 and is essentially insoluble in biological fluids. Within the fluid are low molecular weight oligomeric cyclic dimethylsiloxanes that are relatively water insoluble (less than 50 ppm), and have a relatively short half life in the body, in the order of a few days.

"Bleeding"

Silicone gel consists of an elastomeric polymer which is crosslinked with two carbon bridges. The cohesiveness or solidity of the gel correlates with the extent of crosslinkage. Liquid silicone consists of glucose-linked PDMS polymer chains. It has been found to "bleed" through the envelope of the implant over a period of time (Domanskis and Owsley, 1976; Bergman and van der Ende, 1979).

To reduce "bleed" and also improve the consistency the original gel has been altered, and the silicone envelope changed to include a laminated inner trifluoropropylmethyl silicone elastomer and an outer dimethyl silicone elastomer, or in other instances a phenyl layer of silicone dioxene polymer sandwiched to methyl layers of silicone.

Despite this, minute particles of PDMS are still extruded and are then taken up by the reticuloendothelial system. Slow dispersal of these particles takes place over a period of years, and they have been detected in liver, spleen, kidney, lung, heart and brain in dog studies (Dow Corning Wright, 1992a). There have been several case reports of silicone granulomas occurring locally, and in regional lymph nodes, after implantation of breast prostheses (Ben Hur and Neuman, 1965; Ben Hur *et al.*, 1967; Travis *et al.*, 1985; Truong *et al.*, 1988), and silicone arthroplasty (Rogers *et al.*, 1988).

It has further been noted that saline-filled prostheses also "bleed" from the silicone envelope itself (Vargas, 1979) but to a lesser extent than silicone gel-filled prostheses. No difference however was noted between the contracture rate found with single and double lumen implants (Hartley, 1976).

Teratogenicity

There is no human evidence that disseminated silicones, resulting from "bleed", have any teratogenic effects. Animal studies using large doses of PDMS subcutaneously have been inconclusive (Dow Corning Wright, 1992a). Testing of human milk for PDMS in 6 women after breast augmentation produced no significant difference between test and control groups (Dow Corning Wright, 1992b).

Silicones and the immune system

There has been concern that silicones may not be wholly inert, as originally thought. The development of silicone hypersensitivity has been suggested as an explanation for problems with a variety of silicone implants, *e.g.* the obstruction of cerebrospinal fluid shunts. Granulomas have been found around inserted erecting penile implants and Eustachian tube prostheses, which had failed. However the toxicological implications of a granulomatous reaction are equivocal as both biocompatible and immunogenic materials can elicit the same reaction.

"Silicone synovitis", occurring after the abrasion of joint prostheses against bone surfaces, is believed to be a particle synovitis, related to the size of the particles generated from fibrillation of the solid implants by mechanical abrasion. Similar synovial reaction has been reported with particles derived from other implant materials, and it has been suggested that 10–60 μm particles may be particularly reactive. However, it was not felt on a review of all the initial reports of this condition that there was any evidence of autoimmune disease (Chase, 1985, cited in Sergott *et al.*, 1986).

Free PDMS in tissue is characterised by a lymphohistiocytic infiltrate with foreign body giant cells. The granulomatous infiltration may be due to an immunologically mediated reaction against a silicone-associated antigen.

Small molecular weight chemicals, lipids and nucleic acids are not generally immunogenic, but can, when conjugated to an immunogenic protein carrier, behave as a hapten to stimulate specific antibodies.

Silicones are known to bind proteins and show only slow, partial exchange of absorbed and dissolved protein (Brash and Uniyal, 1979). Delayed hypersensitivity to a silicone-protein complex has been demonstrated in the guinea pig model (Kossovsky, 1986). In this study serum was mixed with PDMS, but the interpretation of these results has been criticised on the grounds that the serum was derived from an outbred strain of guinea pig, and an immunological reaction is known to occur to outbred serum alone. The induction of delayed hypersensitivity has not been corroborated in recent rat studies (Brantley *et al.*, 1990).

Adjuvant disease

A new disease entity was created in 1954 when polyarthritis was induced in rats after subcutaneous injection of spleen cells with Freund's complete adjuvant (dispersed heat-killed tubercle bacilli in mineral oil) (Stoerk *et al.*, 1954), and by injection of Freund's complete adjuvant alone (Pearson, 1956). This experimental "Adjuvant Disease" occurred one week after injection, with ulceration at the injection site, acute periarthritis distally several days later, and then nodular skin changes, chronic arthritis, uveitis and iritis, weight loss, malaise and hair loss.

There are similarities between the manifestations of experimental Adjuvant Disease, and clinical rheumatoid arthritis in humans. It is believed that experimental Adjuvant Disease is a delayed hypersensitivity reaction to a specific part of the bacterial cell wall. An exact equivalent of Adjuvant Disease has not been described in humans, even though the term "Human Adjuvant Disease" has gained wide currency.

"Human adjuvant disease"

The term "Human Adjuvant Disease" was used by Miyoshi *et al.* (1964, cited by Sergott *et al.*, 1986) when reporting two patients who developed a clinical picture similar to rheumatoid arthritis after receiving paraffin injections for breast augmentation. Both patients had hypergammaglobulinaemias associated with polyarthritis, and showed improvement following mastectomy.

Similar reports followed (Kumagai *et al.*, 1979) with epidemiological evidence suggesting that the relationship between the syndrome, and prior injection with foreign substances was not due to chance.

A further review of 46 patients (Kumagai *et al.*, 1984) detailed signs and symptoms of connective tissue disease following injection of paraffin or silicone. Two groups of patients were described. About half of the patients presented with features consistent with a recognised connective tissue disease, the commonest being systemic sclerosis (scleroderma). Systemic lupus erythematosus, rheumatoid arthritis, Sjøgren's syndrome and Hashimoto's thyroiditis were also seen. Patients in the second group had clinical and laboratory abnormalities suggestive of connective tissue disease but did not manifest a pattern falling into any specific diagnostic group. The patients in this group were described as having "Human Adjuvant Disease".

In 1982, Van Nunen *et al.* described 3 patients showing autoimmune syndromes following breast augmentation with gel-filled prostheses and other reports involved both gel-filled (Baldwin, 1983) and saline filled implants (Vargas, 1979; Byron *et al.*, 1984). The "Human Adjuvant Disease" entity has therefore been linked to paraffin injection, silicone injection (Fock *et al.*, 1984), combined silicone and paraffin injections (Okano *et al.*, 1984), as well as gel and saline filled implants.

Free silica (such as encountered in industrial exposure to silica) is a potent stimulus to inflammation. There is disagreement as to whether it has antigenic potential as suggested by some authors (Heggers *et al.*, 1983), whilst other workers have associated it with the

development of auto-antibodies, and connective tissue disease including systemic lupus erythematosus and scleroderma (Rodnan *et al.*, 1967).

Attempts have therefore been made to explain the aetiology of "Human Adjuvant Disease" on an immunological basis. One such theory refers to the presence within implant shells of 30% silicon dioxide (silica) as a filler. Silica and silicone are physically, chemically and immunologically distinct and are not comparable in their biological behaviour. The silicon dioxide within implants is chemically fused to the silicone polymer and does not have the same reactivity as free silica. However, suggestions have been made as to how silica may be liberated from its bond to silicone, for example following macrophage phagocytosis (Vargas, 1979), but clearly documented evidence has yet to be presented.

Although involving only a small number of patients, there is now a recognition that the presence of silicone-based implants may be associated with autoimmune phenomena. To clarify this association, and to establish whether there is indeed a causal relationship, any suspected "Human Adjuvant Disease" occurrences need to be fully investigated according to stringent criteria, as outlined by Sergott *et al.* (1986).

The reporting and further study of these cases might ultimately lead to the identification of a susceptible patient population. HLA typing may be useful in this respect. Unlike several other autoimmune diseases however, no association has yet been established between the clinical presentation of "Human Adjuvant Disease" and any defined HLA haplotype.

Evidence against the positive immunogenic activity of silicones has also been presented (Wilsnack and Bernadyn, 1979; Brantley *et al.*, 1990). In these rat studies, sensitised animals showed no alteration in lymphocyte subpopulations or lymphocyte activity after being rechallenged. It has been shown that macrophage ingestion does lead to cytoplasmic transfer of silicone to lymphocytes (Maekawa *et al.*, 1984). The same study also found silicone inhibited macrophage migration to less than 45% of expected. In addition a study of the aetiology of implant infection found that the ability to generate superoxides, and the ingestion rates of polymorphonucleocytes, were reduced by 72% and 25% respectively when in the vicinity of an implanted foreign body (Zimmerli *et al.*, 1984).

Our understanding of the interaction of silicone with the immune system is far from complete. If the biological response to silicone is simply a non-specific reaction not involving antigen recognition by lymphocytes, some clinical features might still be explicable. A causal relationship between the presence of silicone breast implants and "Human Adjuvant Disease" has yet to be unequivocally established though it has been suggested (Baldwin and Kaplan, 1983) that symptomatic improvement is seen following removal of the implant. However, both gel and saline filled implants are subject to bleed, and explantation of the implant does not deal with migrated particles distant from the primary implant site and totally remove antigenic stimulus. It is therefore difficult to know why such improvement should be seen.

Silicones and carcinogenesis

Oppenheimer *et al.* (1955) described the induction of tumours in rodents by insoluble solid material introduced subcutaneously. The "Oppenheimer effect" is seen principally with in-bred rodent strains and has more lately been described as "solid state carcinogenesis" to differentiate it from chemical carcinogenesis.

A 1987 study by implant manufacturers Dow Corning indicated that silicone gels implanted subcutaneously in rats produced an increase in the rate of fibrosarcomas at the implantation sites when compared with controls. Metastases were noted in a number of animals. Similar effects have been seen with polymers such as polyurethane and polytetrafluoroethylene (Memoli *et al.*, 1986).

It has been questioned whether the silicone fibrosarcomas were the result of solid state carcinogenesis, or chemical carcinogenesis related to the silicone itself or a product of its degradation.

Silicone associated fibrosarcomas have never been seen in animals higher in development than rats (Hoopes *et al.*, 1967; Lilla and Vistnes, 1976). In these animals they were always seen to occur in tissue which had been in direct contact with implanted materials. No increase in the overall incidence of breast sarcomas has been seen in the US over the period that breast implants have been in use (May and Stroup, 1991) and there has been no reported case of any such tumour occurring in association with implanted material in the breast.

Any question of carcinogenicity must be viewed against the normal background incidence of cancer incidence in humans, and specifically (with regard to breast implants), the high incidence of breast carcinoma in Western women (1 in 10 in the USA, and 1 in 12 in the UK). There have been individual reports of breast carcinoma developing after breast augmentation with implants (Hoopes *et al.*, 1967; Bower and Radlauer, 1969; Benavent, 1973), but a causal relationship has never been demonstrated.

Silicone has been reported to affect lymphocyte function (Zimmerli, 1984), and a reduction in the efficiency of the immunological tumour surveillance mechanism has been postulated as a means by which silicone-induced carcinogenesis might theoretically occur in humans.

However, there have also been reports of anti-tumour effects of silicone gel and elastomer in rats (Dreyfuss *et al.*, 1987) which were thought to have resulted from a reduction in the effects of chemical carcinogenesis. Most importantly, several epidemiological studies of groups of women following breast augmentation have shown no difference in the incidence of breast carcinoma (Harris, 1961; Pangman, 1965; De Cholnoky, 1970). The largest of these studies (Deapen *et al.*, 1986) involved 3111 women followed for a median of 6.2 years and reported a lower than expected incidence of breast carcinoma in augmented women below the age of 40 compared with a control group. This study has continued and following a median follow-up period of 10.5 years, further reports

have confirmed the results of the original paper (Szycher and Siciliano, 1991b).

The suggestion that this group of women was less susceptible to carcinoma merely because of smaller breast mass (as evidenced by their request for breast augmentation) is not fully supported in the reported literature (Wynder *et al.*, 1960; Valaoras *et al.*, 1969).

Polyurethane

Polyurethane covered breast implants were originally introduced as a means of salvaging capsular contractures following breast reconstruction (Ashley, 1970, 1972), and were then recommended for routine use in cosmetic augmentation (Herman, 1984) because of the low observed rate of capsular contracture.

However, clinical satisfaction with the use of polyurethane covered breast implants has been mixed. A large series of 1510 patients was reported by Hester *et al.* (1988) with an overall capsule contracture rate of 7.4%. This success has not been universal. There have been reports of skin lesions and chronic breast pain (Jabaley and Das, 1986), associated with difficulty in implant removal (Cocke *et al.*, 1975), as well as chronic infected granuloma formation with skin reaction (Berrino *et al.*, 1986).

It was initially believed that the lack of capsular contracture was due to microencapsulation of particles of polyurethane following peripheral degradation and phagocytosis of polyurethane fragments as scar tissue grew into the foam coating of the implant. The microencapsulation was felt to dissipate the myofibroblast contractile forces (Lilla and Vistnes, 1976; Slade and Peterson, 1982; Brand, 1984).

Support for this suggestion was derived from histological slides of excised capsules which showed giant cells surrounding fragments of foreign material (thought to be polyurethane) within the area of tissue infiltration. The observation was also made that one week after insertion, or later, removal of polyurethane-coated implants was very difficult and resulted in a significant proportion of the coat being left behind as it sheared from the underlying silicone layer (Berrino *et al.*, 1986).

This fragmentation and dissolution of the polyurethane foam was noted to be accompanied by the accumulation of a brown pigment which gave a positive reaction for haemosiderin (Šmahel, 1978) and was felt to be in the greater part a degradation product of polyurethane (Cocke *et al.*, 1975). Fragmentation was reported at 2 years by Šmahel (1978), but the process may still be incomplete at nine years (Slade and Peterson, 1982).

This apparent inconsistency was explained by Szycher and Siciliano (1991b) when they enzymatically digested the removed tissue capsule and found that the polyurethane foam was intact and could be recovered. They suggested that in previous studies, transverse histological sectioning of the capsule had cut the heavily infiltrated polyurethane foam structure in such a way that interpretation of the resulting sections, in two dimensions only, gave the impression that the polyurethane had fragmented and was being phagocytosed, whilst still in fact remaining intact.

Indeed, if hydrolysis of all the foam were possible, as suggested, there would be profound implications for carcinogenesis because of the *in vivo* generation of 2,4 toluene diamine, a known carcinogen, as the end result of that process.

Carcinogenesis and the chemistry of polyurethane

The large family of polymers called polyurethanes covers a wide range of structural forms, with both clinical and non-clinical applications. Product presentations include foams, rubbers, fibres, adhesives and coating materials as well as thermoplastic materials. Polyurethanes are extensively used in artificial hearts, intra-aortic balloons, diagnostic and therapeutic catheters and many other implantable prostheses.

There is no firm evidence linking polyurethane with carcinogenesis in humans. Even in animal studies, the incidence of polyurethane induced solid state cancers is less than that seen with other polymers in rodents (Brand, 1988). In this study, polyurethane implants resulted in no tumours, smooth silicone implants had an incidence close to 30%, polyvinylchlorideacetate plates had an incidence close to 95%, glass plates had an incidence of around 70%, and no tumours were seen with Millipore® filter discs (Millipore Limited, UK) with pore sizes above 0.1 microns, or with Ivalon® sponge (polyvinylacetate sponge, Ivalon USA, Prosthex UK Limited).

Polyurethane products are derived from chemicals which contain isocyanate groups and di-isocyanates. The particular polyurethane used in breast prostheses is a polyester type made from 2,4 and 2,6 toluene di-isocyanate in a ratio of 4:1. This polyester is then reacted over a catalyst with a polyfunctional reactant, a polyol, to give a cross-linked urethane, a polyurethane. This combination is known to decompose at about 220°C or can be hydrolysed by boiling the substance under pressure at 150°C in 3.0 N sodium hydroxide to produce 2,4 toluene diamine (TDA) as well as methylene dianilene (MDA). Polyurethane will also degrade if subjected to high pH aqueous solution.

Other biomaterials in common usage can also degrade under extreme conditions to give toxic products. Polytetrafluroethylene (PTFE) if burned, produces hydrofluoric acid, and PVC releases hydrochloric acid when heated.

The degree to which hydrolysis occurs *in vivo* is disputed, but the answer is central to establishing the safety of this material, as a possible mechanism of cancer induction by polyurethane would be through the *in vivo* production of toluene diamine (TDA), a known chemical carcinogen in animals.

To ascertain if TDA is produced in quantity by the enzymatic degradation of this particular type of polyurethane foam, Szycher and Siciliano (1991a) performed an *in vitro* test, simulating physiological conditions as closely as possible. In these tests TDA was formed in the first 4 days, reaching a maximum of 8.3 parts per million. After the initial burst no further TDA was observed within the limits of detection of the experiment (10 parts per billion). Based on a standard risk assessment, this amount of TDA translates into a

risk of developing cancer of one in four hundred million.

It should be remembered that 1 in 12 women is at risk of developing breast cancer in her lifetime, so that the increased risk of developing a malignancy due to TDA release has to be considered to be insignificant.

Practical applications

Capsular contracture

With the implantation of non-toxic, sterile material which cannot be phagocytosed because of size, an encircling scar or capsule is produced by the proliferation of fibroblasts to contain the foreign body. Breast augmentation capsules are known to contract, and this can result in a poor cosmetic outcome.

Identification of this problem with the original smooth walled (or "slick") implants led to many efforts to reduce capsular contraction rates which, with the original prostheses, gave a 30–50 % incidence of Baker III and IV capsular contractions (McGrath and Burkhardt, 1984; Coleman *et al.*, 1991; Ersek, 1991).

The use of textured silicone implants has reduced the incidence of capsular contraction when compared with the incidence seen with smooth implants (Coleman *et al.*, 1991). A similar improvement in contracture rates had previously been seen with the introduction of polyurethane-coated implants in 1970 (Ashley, 1970, 1972; Capozzi and Pennisi, 1981). These reductions in capsular contracture rates are likely to be due to the irregularity of the prosthesis/host interface and the ability of irregular surfaces to break the action of fibroblast contact guidance (Peacock and Van Winkle, 1970), producing a multiplanar orientation of collagen fibres and non-linear contraction within the capsule.

Mammography

It has been known for many years that the quality of mammography images is altered following augmentation mammaplasty, and there has been concern that this might lead to delayed detection of breast cancer with an adverse effect on survival.

All currently available breast implants are radio-opaque, but to varying degrees, and may obscure a proportion of the breast tissue (Hayes *et al.*, 1988). During mammography, the presence of the implant causes compression of the adjacent soft tissues, and produces a denser, more homogenous picture of the breast tissue, which can make the detection of lesions difficult.

There have been reports of breast implants rupture by the compressing plates of the mammography machines. A further concern with breast augmentation is the incidence of mineralisation around the implant shell, which can lead to misleading results when the degree of calcification is marked. Mineralisation is present around breast implants in between 17 % (Inoue *et al.*, 1983) and 32 % of patients (Rolland *et al.*, 1989).

Attempts to produce a more radiolucent implant have continued, and the radiolucency of various types of implant has been tested using phantom artifacts (Young *et al.*, 1991). Silicone shells of all types were shown to affect detection minimally, whilst polyurethane-coated implants obscured a proportion of the test artifacts. Saline or silicone-gel filled implants were radio-opaque, but silicone shells filled with peanut oil or sunflower oil were radiolucent and allowed ready detection of the phantom artifacts used. Further studies are under way to achieve a breast implant and filler that still offers a satisfactory cosmetic result but with improved radiolucency. A radiolucent implant with a bio-oncotic gel filler has recently been withdrawn (Laing and Sanders, 1991).

Mammography remains a valuable investigation in the early detection of breast cancer when carried out by an experienced radiologist, aware of the presence of breast implants, and able to use displacement techniques (Eklund *et al.*, 1988). In large cohort studies of women who had had implants it was found that previous breast augmentation surgery did not adversely influence the stage of disease at diagnosis (Deapen *et al.*, 1986; Mitnick *et al.*, 1989).

Conclusions

There is evidence to suggest that in a very small proportion of patients there may be an adverse systemic effect following implantation of synthetic materials, the degree and predictability of which should be the subject of further study. "Human Adjuvant Disease" is not the same entity as experimental Adjuvant Disease, and may not be a single defined condition, the onset of which can be precisely linked to the previous insertion of breast implants, in the same way that the experimental disease can be linked temporally to adjuvant injections.

Further work is also necessary to clarify the possible immunological and biological effects of implanted materials, and their physical and biochemical behaviour *in vivo*. The manufacture of polyurethane covered breast implants has been suspended.

There is no firm evidence linking breast augmentation with human carcinogenesis. However, it may be considered that if there is any such risk, the time from implantation to presentation is likely to be great, as seen in other foreign body associated tumours (*e.g.* asbestosis and schistosomiasis). Studies such as those of Deapen *et al.* (1986) are important and should continue, and there is a need for a comprehensive and accurate surveillance programme to put this question beyond doubt.

The problem of peri-implant capsular contracture has been largely overcome with the introduction of rough textured silicone implants. The long term problems associated with polyurethane foam coated implants are well recognised, and these implants are no longer manufactured.

The presence of an implant may compress overlying fat, and distort underlying breast tissue, but the careful use of displacement techniques will allow adequate visualisation and interpretation of mammography films.

On January 6 1992 the US Food and Drug Administration (FDA) announced a 45 day moratorium on

the use of silicone gel breast implants within the United States, pending the review of new information. Saline filled breast implants continue to remain available.

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Paper received 13 January 1992.
Accepted 11 February 1992, after revision.