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Silicon and matrix macromolecules: new research opportunities for old diseases from analysis of potential mechanisms of breast implant toxicity

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Abstract — An understanding of the normal and essential integration of the element silicon in biosystems, as well as knowledge of its fundamental chemistry, are crucial to understanding its role in health and disease. Modern organosilicon chemistry, based in part on the artificial silicon–carbon bond, coincided with the emergence of the biomaterials and bioengineering fields fifty years ago, and was thought to be a fortunate coincidence according to conventional wisdom that high-molecular-weight polymeric siloxanes were chemically and biologically inert. These concepts have been challenged by reports of silicone migration and degradation following insertion of gel-filled breast implants, claims of a novel systemic illness appearing in many breast implant recipients, and investigations implicating varied and permeating immunotoxic mechanisms of disease causation by breast devices. The present study develops additional potential pathogenetic ideas based on alterations of cell biochemistry by silicon-containing compounds, and offers correlation of the patients' diverse clinical features with plausable disruption of basic biological processes. This in turn raises new questions concerning everyday environmental exposure, has broad implications for multiple other diseases, can provide alternative directions for future investigative research, and may contribute to the ongoing redefinition of immune dysfunction and inflammation.

Silicon biochemistry and essentiality

Silicon (Si) is the second most abundant element in the earth's upper crust, second only to oxygen (O), to which it is usually bound in nature rather than existing free in its elemental form (1). Under ordinary circumstances, silicon, like carbon, is capable of forming four bonds, and both are known for their ability to polymerize and form network covalent structures (1,2). However, unlike carbon, silicon does not usually form stable bonds to itself (1,2). Silica (silicon dioxide, or SiO_2) consists of two double-bonded oxygens to silicon, and is found in amorphous and crystalline forms. The amorphous forms include natural and synthetic glasses and fumed fillers in many consumer products (3). Crystalline

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silica in the form of quartz is the most abundant mineral in the earth's crust, and is essentially a dehydrated hard igneous rock formed by high temperature and pressure processes (1). Other forms of crystalline silica include cristobalite and tridymite (3). Silicates are minerals composed of silicon, oxygen and other ions (K, Na, Ca, Mg, Fe, Al, P, etc.), and are also part of most rocks on the earth's surface (1,3). Some nonfibrous (crystalline) forms of silicates include feldspar, talc, mica, vermiculite, and bentonite, while fibrous forms include all the asbestos compounds (1,3).

The upper crust layer above the mantle of the earth consists of igneous rocks, sedimentary rocks, hydrosphere (oceans, ice, rivers, lakes, water vapor), and atmosphere (air) (1). Igneous rocks are rocks which have been formed by a melting process caused by high temperature and pressure. Silicon content in igneous rocks is very high (1). The most silicon rich rocks are designated as acidic (e.g. granite, quartz), while those poorer in silicon, which also contain much magnesium and calcium oxide, are designated as basic (e.g. diorite, gabbro). Sedimentary rocks consist of three main types: limestone, shale, and sandstone (1). These contain the common minerals like feldspar and quartz, and also contain dolomite, calcite, and hemotite. The silicon content of sedimentary rocks is also high (1).

The hydrosphere acts as a link and balance between the igneous rocks and the sedimentary rocks by the natural process of chemical weathering. In this process, silicon in various forms is leached out and transported via rivers and streams from the igneous rocks of the continents to the oceans, where water, carbon dioxide, and hydrochloric acid are added along the way (1). As the sediments grow in thickness, they sink deeper and deeper into the sea bottom, where temperatures increase and mixing with magma occurs, and eventually they rise up to the surface forming new mountains and continents. The entire weathering process releases free solid silica which, in the presence of water, produces monosilicic acid (1):

$$SiO_2 + 2H_2O \rightarrow Si(OH)_4$$

This is true for any of the forms of silica, amorphous or crystalline (1). The rate of reaction depends only on the temperature, pressure, and the nature of the solid silica phase. The –OH group attached to silicon is called a silanol. Silicon in natural waters exists mainly as monosilicic acid (1). Despite varying concentrations in drinking waters in different municipalities and countries, human serum concentrations of silicon remain the same in the presence of normal renal function (1,3).

The emergence of silicon-metabolizing biological systems five hundred to six hundred million years ago, especially in diatoms (unicellular algae), resulted in a drastic alteration of the concentration of dissolved silica in the oceans, which eventually reached a balance (1). For these organisms silicon was and still is essential for virtually any and all cellular functions, including DNA synthesis, energy production, and cell wall structure (1). During the subsequent complex and long evolutionary process a choice was made between phosphorus and silicon, and the original primitive formation of organic silicate esters gave way to present-day sulfate and phosphorate esters (1). The net result was that the older pathways have long since been abandoned by the higher organisms. Thus, part of the intracellular capability to recycle silicon in this globally crucial and integrated biochemical manner appears to have been lost.

This is not inconsistent with current knowledge that silicon is essential to normal growth and development. It should be noted, however, that the organic derivatives of silicates that have functional significance in man contain silicon bonds linked to oxygen, not carbon (1). There is a biological need for silicon, beginning with embryologic development of connective tissues and subsequently encompassing maintenance of the same (1,4). It has been known for over two decades that silicon, calcium, phosphorus, and magnesium accumulate in the mitochondria of osteoblasts before any evidence of extracellular ossification occurs (1,4). Silicon deficiency in animals causes reduced mineralization of bone, reduced collagen content of bone, reduced skeletal growth, bone deformities, thinner articular cartilage, smaller and less well-formed joints, and adverse effects on skin, hair, nails, and mucous membranes (1,4). Under normal conditions, silicon is found in highest concentration in the aorta, trachea, tendons, ligaments, bone, cartilage, skin, dental enamel, cornea, and sclera (1,3). For these areas and all other connective tissue sites throughout the body, the proteins in the solid phase extracellular matrix containing covalently bound carbohydrates are classified into three categories: glycoproteins, collagens, and proteoglycans. For proteoglycans, the major carbohydrate component is a glycosaminoglycan, which is an unbranched long chain that is highly sulfated and has a motif of a disaccharide repeat (5). Examples are keratan sulfate, chondroitin sulfate, hyaluronan, dermatan sulfate, heparin, and heparan sulfate. Silicon provides links within and between polysaccharide chains of glycosaminoglycans, and helps link the glycosaminoglycans to their respective proteins (1,4). Types II and IX collagens are also known to contain bound glycosaminoglycan chains. Glycoproteins are formed when

sugars such as mannose, fucose, galactose, sialic acid, and N-acetylglucosamine are linked to proteins in oligosaccharide units (6). All of these matrix components are adhesives, acting as glues by binding to each other. Thus, in an extracellular locale, silicon contributes to the architecture, form, strength, and resilience of connective tissues.

The solid phase extracellular matrix is also involved in storing, binding, protecting, and releasing many regulatory agents. All hormones, growth factors, gases, waste disposal, and nutrients must penetrate or pass through the matrix in moving from one tissue or compartment to another. Matrix components can select, inhibit, facilitate, and remove molecules with which they come in contact. For intercellular exchanges of information (e.g. neural transmission), the role of the matrix must be considered.

The classic extracellular matrix macromolecules are chemically similar to macromolecules found on cell surfaces, and as such are integral membrane components as well (5). The cell membrane bilayer of phospholipids acts as a solvent for integral membrane proteins which can diffuse laterally in this milieu. The attached sugar residues on these proteins are always located on the extracellular side of the plasma membrane (6). These carbohydrates are information-rich molecules, and their diversity and complexity confers a variety of important functional characteristics. Examples in the proteoglycan category include syndecan, aggrecan, decorin, versican, biglycan, and glypican, with known functions as receptors, adhesion molecules, signal transducers, inhibitors, regulators, and epithelial cell layer stabilizers (5).

Other cell surface proteins are intermittently linked to glycosaminoglycans and are termed part-time proteoglycans. Examples include thrombomodulin (an endothelial cell membrane proteoglycan that interacts with protein C and thrombin to influence coagulation), betaglycan (receptor for transforming growth factor B), and CD44 (hyaluronan receptor, lymphocyte homing receptor) (5). The CD44 receptor mediates specific adhesion of lymphocytes to high endothelial venules in lymph nodes. It has a wide distribution, and is expressed in brain, medullary thymocytes, B cells, monocytes, mature T cells, fibroblasts, granulocytes, erythrocytes, keratinocytes, and carcinoma cell lines. Some of the solid phase and cell surface proteoglycans are also known to be soluble in the body (i.e. exist in blood or tissue fluids), such as aggrecan, decorin, glypican, hyaluronan, betaglycan, and syndecan. Hyaluronan is involved in varied biologic processes ranging from embryonic development to wound healing. On the cell surface, betaglycan enhances signal responsiveness to TGF-B, but in the soluble matrix phase it is an antagonist.

By inference, silicon can be expected to be present in all of the proteoglycan macromolecules discussed so far. Even the basement membrane (cell lamina) is likely to incorporate silicon in its structure. This matrix, which is noncovalently linked to the plasma membrane of most animal cells, is present over most of the surface of muscle cells (smooth, cardiac, and skeletal), fat cells, Schwann cells, and the basal surface of most epithelial cells (5). The basement membrane contains at least one proteoglycan, perlecan, which contains the glycosaminoglycan heparan sulfate. The cell lamina is intimately involved with active exchange in and out of the cell, filters and protects the surface of the cell, and provides temporary binding and/or storage of a variety of regulators and growth factors. Signals from the synaptic cell lamina of muscle cause acetylcholine receptor genes to transcribe agrin (which contains three laminin modules). Secretion of agrin results in interaction with proteoglycans, inducing aggregation of the acetylcholine receptors at the neuromuscular junction. Perlecan also interacts with platelet-derived growth factor and dampens its stimulation of smooth muscle replication. In the fluid phase, heparan sulfate can inhibit fibroblast growth factor binding to fibroblast receptors.

Glycosaminoglycans are also present in secretory granules inside mast cells, the latter of which are found in or around alveoli, bowel mucosa, dermis, nasal and conjunctival mucosa, synovium, blood vessels, and bronchioles (5). Preformed mediators such as tryptase are stored inside secretory granules bound to heparin, in close proximity to chondroitin sulfate E. Mast cells secrete serglycin, a proteoglycan also made by all other types of hematopoetic cells (including natural killer cells), which stores and protects a variety of agonists with which it is co-packaged. For the mast cell this includes histamine, and, when taken in its entirety, serglycin clearly is involved in regulating the release and rates of degradation of all sorts of bioactive reagents responsible for inflammation, immune responses, and coagulation. In this regard it is interesting to note that suppression of natural killer cell activity has been reported in patients with silicone gel breast implant toxicity, with reversal of this dysfunction following explantation (7).

Glycoproteins are equally pervasive in their functional importance, and mediate many biological recognition processes (5). Glycoprotein receptors in the cell membrane of platelets are intimately involved in adhesion and activation. Thrombospondin (a glycoprotein found in platelets and other cells) influences fibrin formation and lysis by inhibiting plasmin. Laminin bound to adhesion molecules of endothelial

cells is in turn bound to type IV collagen by entactin (a glycoprotein that is a major constituent of basement membranes). Proteolytic fragments of the laminin alpha chain are chemotactic for mast cells. The majority of cell surface receptors mediating endocytosis are transmembrane glycoproteins (6). Apolipoproteins are glycoproteins that not only solubilize lipoprotein constituents but also hold the key function for their metabolic fate by interacting with enzymes and cell membrane receptors. Endothelial cell surface receptors for oxidized LDL are complemented by lipoprotein lipase bound to heparan sulfates. Indeed, the comingling of numerous glycoprotein and proteoglycan molecules on the surface of endothelial cells enables these cells to perform a wide variety of critical physiologic functions by interacting with (a) cellular and soluble blood components, (b) other cells in the vascular wall, (c) solid phase matrix components, and (d) multiple cytokines, the latter of which can upregulate other adhesion molecules (selectins, integrins, etc.). The carbohydrate-binding adhesion molecules known as selectins are similar to the carbohydrate-binding proteins of *E. coli* called lectins, which enable the bacteria to adhere to epithelial cells of the GI tract. This highly preserved evolutionary mechanism forms the basis for some viruses to gain entry into host cells, and for the CD44 ligand. Adhesins are surface molecules expressed by other microorganisms that use the matrix as a substrate to establish infection. As an example, both pneumocystis and aspergillus bind to fibronectin, a glycoprotein that has affinities for collagen, fibrin, heparin, thrombospondin, integrins, and components of bacterial cell walls, and which forms a substrate for repair cells to adhere to in wound healing. During angiogenesis (neovascularization), if anchorage-dependent endothelial cell spreading and migration is inhibited, apoptosis is triggered. Apoptosis has recently been reported to occur when anti-cardiolipin antibodies bind to membrane complexes of phosphatidylserine and B_2 glycoprotein (8).

From the preceding discussion it can be appreciated that despite losing its role in energy production and DNA synthesis, silicon biointegration remains quite extensive in that it is intimately involved with macromolecules displaying endless variations of complex overlapping interactions. It also seems logical that silicon (like growth factors, cytokines, hormones, and vitamins) should impact on matrix regulation, contributing to the circuitous observation that the matrix itself is directly and indirectly involved in feedback on its own production, polymerization, degradation and recycling.

Environmental pervasiveness and bioactivity

Perhaps one of the most striking facts regarding the biochemistry of silicon is that virtually no silicon–carbon, silicon–hydrogen, or silicon–silicon bonds have been detected in nature (1,2). But over fifty thousand such compounds were synthesized during the last century in many laboratories, and form the basis of modern organosilicon chemistry. These molecules essentially contain organic substituents bound to silicon through the silicon–carbon bond. Common silicon-containing products include fluids oils, rubbers, plastics, resins for impregnation of paper and fabrics, glass, cosmetics, lacquer, paint, varnish, adhesives, sealers, antistick agents, antifoam agents, water repellants, insulation materials, household abrasives, beer, insect repellants, pesticides, insecticides, and other poisons. These latter three items are comparable to strychnine and can cause muscle twitching, convulsions, fever, tremors, respiratory depression, paralysis, and altered coagulation (1). Other products increase the yield and quality of crops, increase the weight of fowl, increase egg production, serve as food additives (e.g. spices, powdered sugar, dried eggs), coat fruits to prevent bruising, and aid in food processing. Biologically active organosilicon compounds with everyday medical uses are myriad, and include antomicrobials, psychotropic drugs, anticonvulsants, antitumor agents, wound and burn ointments, skin coverings to promote faster healing, antiflatulants, antiulcer agents, and allopecia preparations (1). Some of these products contain silicones and have the ability to modulate hormonal, endorinologic, and neurotransmitter functions. Other widespread applications of this technology include intravenous tubing, cardiac pacemaker lead tips, heart valves, cerebrospinal fluid shunt tubing, digital joint arthroplasty prostheses, vitreous replacements, lens implants, contact lenses, syringe lubrication, nasal and mandibular reconstruction devices, dental impression materials, and breast implants, All of the products in this last category are composed of silicones.

The obvious question to be asked, then, as more and more of these products proliferate for routine commercial use is: in which way will living organisms react if they are confronted with artificial organosilicon compounds? The in-vivo chemistry evolved by biological systems is different from the chemistry of man's ingenuity. Although chemists have collected a great deal of physical data on the strength, energy, polarization, rearrangement, and stability of the various bonds of these artificial mole-

cules, anticipated or unanticipated biodegradation may subsequently be followed by novel and unanticipated biointegration. Thus, an advantageous quality in theory may turn out to be disadvantageous in reality, As an example, by 1977 several artificial organosilicon compounds were already known to be capable of serving as the sole energy source for many bacteria (1). These substrates, when broken down, do not necessarily result in the release of free silicon as an end product. Because such compounds are a carbon source for growth, smaller residual silicon-containing molecules may be rearranged and/or redirected for anabolic utilization, with subsequent adverse physiological implications. During the degradation of these compounds, intermediates can be formed with one or more free Si–O groups, which inherently have a tendency to react with each other (1). This chemical reconstitution is not simply the reverse direction of the original degradation. Biological systems are far from homogeneous, and locally concentrated silicon can form polymerized species of unknown crystal forms (i.e. silicates) by interacting with calcium, magnesium, and phosphorus (1). In this regard, the reported presence of magnesium silicate (talc) in periprosthetic breast tissues may have profound importance, and is worthy of additional study (9). Talc is a known sclerosing agent, is associated with granuloma formation and chronic inflammation, and may also have adjuvant properties in animal models. Biology can also energize systems, and silicates bound to sugars can become catalytically active, taking on the properties of enzymes (1). This phenomenon has direct relevance to the reported observation that the sequential evolution of systemic illness following silicone-gel-filled breast implantation is unique and proceeds in an exponential manner analogous to a reactor catalysis mechanism (10). Alternatively, binding of silicates to the sugars of matrix macromolecules could have multiple other profound consequences.

Problems with silicone-gel-filled breast implants

All of the biochemical data discussed thus far have distinct practical significance in light of observations dealing with silicone-gel-filled breast implants, including: (a) the documented occurrence of gel bleed through an intact elastomer envelope; (b) the uptake of silicone gel by macrophages and other cells; (c) the dispersion of silicone gel to multiple distant body sites; and (d) the in-vivo breakdown of silicone gel to smaller molecules (11–17). But these reports also raise more ominous and fundamental considerations, since from the discussion on matrix macromolecules it would appear that there is a finite limit of adaptive mechanisms by which normal cells and tissues can dispose of excess silicon. After that, biochemical chaos affecting synthesis, polymerization, degradation, and recycling of connective tissue components could ensue, with multiple physiological effects. In multiple cohorts of symptomatic breast implant recipients the skin displays a myriad of prominent findings (10,18–28), implying global connective tissue dysfunction of cells and matrix. What is noted on the outside of the body is likely to be diffusely occurring on the inside. Although the incidence of these patients' systemic symptoms and signs needs to be compared to cohorts of device-free patients with classical connective tissue diseases, the list of phenomena is long and includes (but is not limited to): fatigue, joint pain, bone pain, dry eyes, dry mouth, dry skin, cognitive dysfunction, myalgia, weakness, hair loss, nail changes, skin rashes, paresthesia, dysesthesia, freckling pigment change, headache, dizziness, nausea, foul taste, weight gain, weight loss, bruising, photosensitivity, fever, chills, infections in various tissues and organs, loose stools, constipation, periodontal disease, skin papules, muscle twitching, urinary symptoms, dysphagia, menstrual irregularity, blurry vision, tinnitus drug reactions, emotional lability, insomnia, Raynaud's, edema, hemangiomas, poor wound healing, venous and capillary dilatation and neovascularization (telangiectasias), reduced hearing, reduced smell, tremor, mouth sores, tight skin, dyspnea, wheezing, palpitations, seizures, parotid swelling, heat intolerance, and cancer (10,18–29). As a logical extension of global matrix dysfunction, and considering the diverse constitutional (genetic) make-up of these patients, such a generalized disease process would be expected to exhibit considerable and variable latency, as well as considerable heterogeneity, two of the hallmarks repeatedly emphasized by multiple investigators reporting on the clinical symptomatology of breast implant recipients. It would also explain the general futility noted in treating patients suffering from suspected silicone toxicity with anti-inflammatory medication, since such a mismatch should come as no surprise, and ought to be expected. Indeed, such patients often exhibit marked intolerance to anti-inflammatory and other medications, probably reflecting metabolic imbalance that leaves little room for normal drug utilization (18).

Other biochemical considerations

The question then arises, is silicone-gel-induced disease an extreme form of a more generalized and slower-paced process occurring in the general popula-

tion? The proliferation of man-made silicon-containing compounds has raised the exposure level in everyday life considerably. In addition, prior absorption studies of high-molecular-weight polymeric siloxanes have dealt with urinary excretion studies over days to weeks (1), and they may be fundamentally flawed by not taking into account: (a) the latency of diverse biological processes; (b) the very complicated nature of extraction and identification of organosilicon molecules and/or metabolites from biological material; (c) the possible degradation of dietary organosilicon compounds by gut bacteria, which may enhance absorption and long-term biointegration; and (d) symbiosis disruption, i.e. the possible interference with the conversion (by gut bacteria) of numerous endogenous and exogenous substrates into a wide spectrum of metabolites (e.g. glycosidases that act on excreted liver products to produce B complex vitamins).

Some of these considerations could be studied by applying current knowledge from the rapidly expanding field of geomicrobiology to medicine, which in turn could have important implications for a whole host of medical phenomena and conditions, including asthma, colitis, atherogenesis, senile dementia, aging, thrombosis, osteoarthritis, allergy, neuropathy, lupus, myositis, multiple slcerosis, ovarian cysts, fibromyalgia, chronic fatigue syndrome, Sjögren's syndrome, apoptosis, migraines, Alzheimer's, and cancer. One's scientific curiosity can be further enhanced by considering four pieces of knowledge readily available in 1977 encompassing the interface and interaction of silicon-containing compounds with organic components of biological systems (1). One such reaction was the reasonable expectation that aqueous monosilicic acid, $Si(OH)_4$, like the related compounds boric acid, $B(OH)_3$, and germanic acid, $Ge(OH)_4$, would form strong complexes with organic hydroxy compounds such as polyols, saccharides, and hydroxycarboxylic acid. Indeed, the formation of such Si–O–C bonds had been demonstrated to result from the esterification of organic hydroxyl groups with SiOH groups. A second known fact was that, in water solution, labile bonds are formed between the neutral oxygen or nitrogen atoms of alcohols, ketones, ethers, amides, and amines and the hydrogen atoms of silanol groups, SiOH. The resulting Si–O–H--C hydrogen bonds occur with silica particles as well as polysilicic acid, and can result in denaturation of adsorbed proteins as a result of distortion of the natural molecular conformation. This change in configuration renders the protein unable to fulfill its biological role. Phosphate esters are powerful hydrogen bonding agents, and account for the significant bonding of phospholipids to silica and silicic acid. These observations have direct implications for the interactions of proteins with the fatty acid composition of cell membrane lipid bilayers, thereby potentially adversely affecting membrane permeability, receptors, signal transduction, or other matrix functions. Cell membrane fatty acids exert an antibacterial effect, and are important in maintaining symbiosis between hundreds of bacteria and the epithelium of the oropharynx, vagina, and intestinal tract. Trapping of bacteria in the mucous secretions of the nasopharynx, trachea, and bronchi usually renders the sinuses and lower respiratory tract sterile. Interference with these functions may have significance for the recurrent sinusitis and other infections experienced by implant patients. Thirdly, the chemistry of silicon is much more flexible than that of carbon, as the former behaves at times like a metal and can participate in chelation reactions. An example is the chelation of silicic acid with catecholamines (e.g. dopamine), thereby affecting neurotransmitters. Fourth, polyphosphates (ATP, etc.) are metal ion bound in biological systems, and competition of silicon for phosphorus can occur, with resultant silicate-phosphate compounds. The implications for energy production in mitochondria are obvious.

In light of all that has been presented, there clearly are ample new avenues of scientific investigation that can be explored for old diseases, which in turn could simultaneously verify or refute the assertions that disease induced by silicone-gel-filled breast implants is a novel entity. With the exception of scleroderma, there does not appear to be any rationale for expecting silicone toxicity to translate into well-defined 'textbook' medical conditions such as lupus, etc. The tightening and thickening of the skin in idiopathic systemic sclerosis arise from the accumulation of excess collagen and other extracellular matrix constituents, including glycosaminoglycans (5). Considering that the receptors for fibroblast growth factor and vascular endothelial growth factor are proteoglycans, and considering that one of many sources of growth factors is the mast cell (5), the circuitous pathogenetic mechanisms of silicone toxicity proposed in this report could easily result in unrestrained fibroblast activation. Resultant features of scleroderma need not necessarily resemble classical subtypes. The controversy over high-profile published studies to date (30,31) that purport to show no association between silicone breast implants and classical connective tissue diseases should not just focus on the analysis of multiple flaws, such as study design, data gathering, exclusions, latency, statistical power, disease misclassification, bias, follow-up, control groups, and mortality contribution (32). The first pressing notion should be to dispense with pre-

conceived ideas of how patients should get ill. In this regard it is not surprising that many of the immunotoxic mechanisms reported and/or proposed to be operative in symptomatic breast implant recipients have been subjected to a critical and scathing review (33). Even in classical diseases such as lupus, where immune dysfunction has clearly been demonstrated, novel studies of biochemical and functional abnormalities of lupus T cells have led to the hypothesis that symptoms and signs of lupus are preceded by an early antigen-nonspecific immune response (34). One of the high-profile studies (31) feebly attempted to insert an afterthought by stating it did not even find evidence for an 'atypical' disorder in women with implants. Unfortunately, many of the common symptoms and signs in symptomatic implant recipients (repeatedly emphasized by numerous investigators) were conspicuously overlooked in this particular aspect of the study. As such, other than the chronological data already referred to (10), appropriate prospective controlled studies demonstrating or denying the existence of a unique silicone-induced syndrome are still lacking.

The diversity of silicon-based products on today's international market is the result of over a hundred years of cumulative experience in the synthesis of innumerable organosilicon compounds. Fifty years ago this proliferation coincided with the emergence of the biomaterials and bioengineering fields, and was thought to be a fortunate coincidence according to conventional wisdom that polymeric organosilicon compounds (i.e. siloxanes) in the form of high-molecular-weight silicones were biologically and chemically inert. This 'wisdom' was based on observations of the reported chemical resistance of silicones to degradation by acids and bases as well as resistance to hydrolysis, the small variation in physical properties as a function of temperature, the very low surface tension, the apparent lack of oral absorption of high-molecular-weight polymeric species, and the relatively mild inflammatory and humoral responses seen with low-molecular-weight fluids. Indeed, in a published Nobel Symposium held in 1977, researchers from the Dow Corning Corporation were noted to state that 'such considerations are among those which have influenced the success of silicones as biomaterials where inertness is absolutely required' (1). However, prior experiments by Dow Corning and others in animals tested with orally administered or injected smaller linear siloxanes, cyclic siloxanes, or polydimethylsiloxane fluids or gel, revealed pharmacologic and/or toxicologic effects such as estrogenicity, analgesia, hyperalgesia, weight loss, hepatomegaly, decreased release of hypothalamic catecholamines, male gonadal shrinkage, vacuolization of peripheral blood neutrophils and monocytes, chronic organ inflammation (liver, kidneys, pancreas), and systemic migration to lymph nodes, liver, spleen, lung, kidneys, adrenal glands, pituitary, hypothalamus, and ovaries (1,2,9,32,34–38). In addition, an internal Dow Corning report in 1975 examined endotoxin-induced interferon type I production in mice after pretreatment with various silicones, including octamethyl-cyclotetrasiloxane (D4). D4 was shown to have adjuvant activity when mixed with Dow Corning 360 fluid (medical grade silicone fluid, or DC-360, used in humans) in that it substantially augmented the interferon production to endotoxin over that in the controls (9). This was complemented by another Dow Corning unpublished report in 1974, whereby it was shown that DC-360 had adjuvant effects on humoral immune responses in animals (9). Yet any mention of these observations by the Dow Corning chemists in the 1977 Nobel Symposium was conspicuously absent, despite discussion of D4 in another experiment detailing its augmentation of catalepsy and ptosis in reserpinized mice (1). In other words there was the potential for D4 to possibly interfere with monoamine synthesis. A close analogue of D4, Cisobitan, was without significant effect in this same experiment, but two of its isomers were antagonistic to reserpine (possibly by stimulating monoamine synthesis). These experiments highlighted the unexpected activities of cyclosiloxanes, and demonstrated 'pharmacologic actions not predicted from the activity of known pharmacons' (1).

Unfortunately, in the 1970s these early warning signs did not lead to any large-scale studies of the fate of high-molecular-weight polymeric siloxanes in biological systems, and their half life still remains unknown. Substances were categorized on the basis of intended use, with less consideration for bioavailability, biodegradation, biotransformation, biointegration, or adverse biological activities. It is now clear that high-molecular-weight silicones (along with the multiple other components, contaminants, and impurities found in breast implant devices) are neither chemically nor biologically inert. In addition to examples already cited throughout this paper, there are reports on: (a) local tissue inflammatory and fibrotic reactions to a host of implant materials, including foreign body giant cell granulomas and the presence of numerous cytokines; (b) antibodies to collagen in implant recipients that recognize different epitopes from those seen in patients with SLE or RA; (c) anti-silicone antibodies; (d) T lymphocyte hyper-responsiveness to silica in implant recipients; (e) a higher than expected incidence of antinuclear antibodies in women with breast implants, which increases with duration of implantation and the

appearance of systemic symptoms; (f) induction of plasmacytomas by silicone gel in BALB/c mice, (g) diffusion into intact implants of hydrophobic human constituents, such as triglycerides and other lipids, with the potential for immunomodulating liposome-like structures to be formed; (h) the unexpectedly high presence of subclinical device infections, and their relationship to capsular contracture and clinical complaints; (i) theoretical increased risk of breast cancer in gel implant recipients (with and without polyurethane foam additive); (j) abnormal esophageal motility, and rheumatic complaints with positive antinuclear antibodies (ANA) tests, in children breast fed by women with implants; (k) morphological and behavioral alterations of fibroblasts by silicone polymers; (l) the demonstration that anti-DNA antibodies from some SLE patients bind to phosphorylated polystyrene, raising theoretical implications for silicone behaving as a specific immunogen, leading to cross-reacting immune responses to matrix macromolecules; (m) the association of cancer with silicate fibers (e.g. asbestos); (n) the linkage of silica exposure to systemic lupus and rheumatoid arthritis; (o) other disease entities known to be caused by exposure to crystalline silica dust (e.g. pulmonary fibrosis, nephrotoxicity, scleroderma, macrophage cytotoxicity); (p) the similar reduction of mean plasma serotonin levels in both fibromyalgia patients and symptomatic breast implant recipients compared with normal controls; (q) the increased presence of HLA-DRw53 in both fibromyalgia patients and symptomatic breast implant recipients compared with normal controls and breast implant recipients without symptoms; and (r) the presence of antipolymer antibodies in both fibromyalgia patients and symptomatic breast implant recipients compared with normal controls (2,3,5,9,10,18,32,39,41,42–44,45).

But there has been a far too narrow focus of investigative direction for both classical and non-classical disease states. The evidence put forth thus far by researchers representing numerous disciplines needs to be sorted out, reassessed, and reanalyzed in light of current knowledge of the fundamental molecular basis of life. Silicase, an enzyme that liberates silicic acid from an artificial organic silicic acid compound, is a membrane-bound enzyme found in mitochondria and microsomes of pancreas, stomach, and kidney (1). Its natural substrate is unknown, but it may have a role in transport function. The silicon content of brain, liver, spleen, lung, and lymph nodes increases with age, and high silicon levels are found in the senile plaques of Alzheimer's dementia (in conjunction with amyloid) (1). The silicon content of aorta, skin, thymus, and hair decreases with age (1). In other parts of the universe a very different type of silicon chemistry could have occurred if water solutions were replaced with something else. In another world, silicon might still be a requirement for the structural stability of plants, and the fiber contents of grains might still be found to be proportional to their silicon contents. Diseases in that world, however, might have nothing to do with cell–cell and cell–matrix adhesion phenomena. Here on earth these are basic and highly regulated biological processes that permeate every aspect of life. The molecular determinants for these processes are likely to be profoundly affected by excess silicon occurring from the in-vivo degradation of breast implant components. This in turn could provide the rationale for predicting the potential toxicity of other organosilicon compounds and simultaneously elicit alternative research endeavors for multiple other disease entities.

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