Title: MECHANISMS OF BREAST IMPLANT TOXICITY: WILL THE REAL RINGMASTER PLEASE STAND UP

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Running Head: Breast Implant Toxicity

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Numerous publications in the past five years have supported the assertion that silicone gel-filled breast implants are genuinely capable of causing a novel systemic illness (1-7). Prior claims of a similar nature existed in the 1990’s when controversy first swirled around this issue, but legitimacy at that time was elusive due to faulty methodologies utilized by many investigators (1,4). Chief among them were the presumptive theories of immune-mediated ailments triggered by these devices. Observations promoting these theories back then included (but were not limited to) (a) the demonstration of extensive inflammatory and immunologic responses in the peri-prosthetic breast tissues and axillary lymph nodes, (b) positive antinuclear antibodies in a third of recipients, (c) the evolution of ever-increasing T cell responsiveness to silica associated with prolonged implantation, (d) the demonstration that silicone gel disseminated to multiple distant sites via the process of gel bleed through an intact envelope or shell, and (e) case reports of connective tissue diseases related to these devices (8). Nonetheless, studies in the 1990’s denied the existence of any association between breast implants and autoimmune diseases (28).

Silicone-induced autoimmune theories have recently been resurrected in the form of ASIA (autoinflammatory syndrome induced by adjuvants, or Shoenfeld’s syndrome), which promotes the concept of multi-organ inflammatory responses to silicone gel (3,5-7,9). The deficiencies of ASIA, and the failure of its proponents to consider multiple other mechanisms of disease causation, have been outlined in a recent letter to the editor (10). In order to further elaborate on these deficiencies one must first understand why the supposedly tightly bound and “inert” cohesive gel utilized in the new generations of breast implants undergoes dramatic changes in gel properties over time (11). Breast implants are just one of over 60,000 products composed of organosilicon compounds (12). Everyday environmental exposure to these myriad products typically winds up in garbage dumps where sludge admixes with dirt and soil. Aerobic and anaerobic bacteria in the soil degrade organosilicon compounds into molecules of silica (silicon dioxide), silicic acid, silanols, water, and carbon dioxide (13). It is now known that normal breast tissue is not sterile (14,15). The diversity of bacteria that are present will routinely colonize the outside and inside of implants once they are inserted into the body (14), whereupon the same degradation processes are initiated (13). These processes are augmented by hydrolases released by macrophages, which are also present in abundance outside and inside these devices (8). In concert with systemic disease onset, the resulting microdispersion of silanols, silica, silicic acid, and other silicon-containing breakdown products to distant sites and organs occurs long before device rupture (16,17). Most importantly, this microdispersion has been documented to exist without concurrent inflammation at these distant sites (18). Stated another way, in the absence of extensive rupture-induced gel extravasation to the lung or down fascial planes, inflammation and immune responses to silicone breast implants are typically present only in the local breast milieu and adjacent axillary nodes (and not at distant sites where excess silicon presence is detected) (18).

The widespread dispersion of silicon-containing breakdown products causes a myriad of disruptions to the body’s biochemistry and enzymatic processes (12,13). Clinical ailments in
implant recipients correlate with these phenomena, with examples of typical biochemical disruptions noted below:

a) 75% of my cohort of over 500 implant recipients manifest dry eyes and dry mouth (with markedly abnormal Schirmer tests), but minor salivary (labial) gland biopsies are normal (16). This phenomenon is likely caused by dysfunction of the proteoglycan receptor for acetylcholine in salivary and lacrimal tissues due to excess deposition of the element silicon in matrix macromolecules (12). Complaints of dry skin are equally common.

b) although the element silicon forms four bonds like carbon, silicon behaves like a metal at times. Phosphorus in energy systems is metal-ion bound (12). Therefore, one cannot expect energy production and energy utilization in cells to proceed normally in the presence of excess silicon molecules. Hence, myalgias, fatigue, and weakness occur, but muscle biopsies in my cohort are normal (16).

c) acetylcholine must traverse the matrix at the neuromuscular junction to initiate muscle contraction. Silicon-induced dysfunction of matrix macromolecules can impair this process and also disrupt platelet activation, lymphocyte homing, wound healing, nail growth, and nerve impulse synapse transmission (12).

d) the 18,000 square centimeters of skin is quite rich in matrix macromolecules, which explains why splotchy hypo- and hyper-pigmentation, ink blot freckling, multiple nevi, and a variety of skin rashes are common clinical features in ailing implant recipients (16). In addition, glycosaminoglycans (such as chondroitin sulfate) bind the pre-formed mediators of inflammation in mast cells (12). Dysfunction of these molecules can account for the itching, urticaria, wheezing, and other “allergic” phenomena experienced by implant recipients.

e) synovial fluid analyses from my cohorts' knees reveal less than 1,000 white cells (non-inflammatory). Think of matrix macromolecules in cartilage and substance P in nerves to account for the joint symptoms in implant recipients.

f) silicic acid can cross the blood-brain barrier and chelate catecholamine neurotransmitters (e.g., dopamine) (12). Hence, cognitive dysfunction occurs in the presence of normal brain MRI scans.

g) silanols can adhere to proteins and enzymes via hydrophobic bonding, with multiple adverse biologic effects (13). Silanols can also donate a methyl group to mercury (the latter of which may accumulate in one’s body from other sources), resulting in the very well-known toxic compound methyl mercury (13).

h) over a dozen heavy metals are utilized in the manufacturing process of silicone gel, and these do not fall out of the soup mixture at the end (19). These migrate to distant sites along with the silicone breakdown molecules, and can be detected in ailing recipients by appropriate testing. It is therefore no surprise that 40% of my cohorts develop a metallic taste, which resolves after implant removal (20). Heavy metals adversely affect enzymes, DNA, and leukocyte respiration; can be toxic to muscle, brain, lungs, kidneys, liver, blood, and nerves; and when present in excess amounts can mimic multiple sclerosis, Parkinson’s, Alzheimer’s, and muscular dystrophy (21). Clinical correlates reported in implant recipients include (but are not limited to) hair loss, recurrent infections in a variety of sites, weakness, cognitive dysfunction, or any other nervous system disorder (e.g., paresthesias; dysesthesias; dizziness; gait
imbalance; and abdominal pain, nausea, constipation, and loose stools from dysfunction of the myenteric plexus) (1-7,12,16,20,22).

i) another cause of recurrent infections in implant recipients (sinus, bladder, pharynx, lung, etc.) is related to immune suppression (not immune stimulation), and occurs from impairment of natural killer cell function (23).

j) ailing silicone recipients also develop odor and smell hypersensitivity. Typical phenomena (which were not present prior to implantation) include headaches, nausea, and dizziness on exposure to perfumes, room fresheners, cleansers, deodorants, hairsprays, exhaust fumes, and cigarette smoke. Food and pharmaceutical intolerances may also develop. Essentially, when one becomes ill from one toxic entity, small amounts of toxicity coming from elsewhere are poorly tolerated. Most over-the-counter skin products (e.g., moisturizers, skin softeners, wrinkle removers, and cosmetics) also worsen implant-induced phenomena because these products invariably contain silicones and an emulsifier. The latter ingredient enables deep penetration of these products to the subcutaneous fat, where they can become biointegrated (silicones are naturally lipophilic).

k) symptoms such as chest pain and shortness of breath on exertion represent restrictive defects that occur due to local irritation of ribs, intercostal muscles, and intercostal nerves (16). They often lead to exhaustive cardiopulmonary evaluations which are invariably normal or negative, but nonetheless are erroneously ascribed to serositis of the pleura or pericardium.

In a recent publication Tervaert and colleagues revisit their implant recipients’ clinical manifestations and continue to invoke causation via autoimmune and inflammatory mechanisms (6). This is a gross oversimplification of what is clearly a much more complicated process, and is compounded by a subtle attempt to expand their diagnostic ASIA criteria to be more encompassing (changes that the reader could easily overlook if one did not compare this publication to prior ASIA guidelines) (9). ASIA goes astray because the diverse inflammatory and immune responses to silicone in the local breast environment parallels the development of systemic ailments, but the former does not cause the latter. Stated more simply, the vast majority of silicone-induced ailments emanate from multiple and varied toxic disruptions of the body’s biochemistry and have virtually nothing to do with autoimmunity (12,13,21). Another recent publication by Tervaert and colleagues discusses factors that may contribute to the development of autoantibodies in implant recipients (27). In actuality, the presence or absence of autoantibodies in patients with these devices has no relevance for diagnosing silicone-induced disease (4,16,20,22). In yet another publication Tervaert and colleagues try to prop up their mistakes by publishing a review of comingled conditions (both explicit and/or loosely defined), all of which lack any unifying clinical features but are all supposed to represent silicone-induced toxicity based on a haphazard response to explantation (7). Their “kitchen sink” approach is devoid of even the most basic elements of proper investigative methodology including, but not limited to: chronological disease development over time; rupture versus non-rupture analysis; duration of implantation analysis; a more comprehensive, reproducible and consistent data base for recording the ailments of their patients; prior exchange surgeries; intrinsic validity analysis; explantation results that take into account the duration of prior implantation; and the well-known fact that a patient fulfilling criteria for a classical connective
tissue disease doesn’t necessarily imply that one has arrived at the correct diagnosis (16,20). Tervaert and colleagues are genuinely and correctly convinced that silicone gel-filled breast implants are capable of causing a novel systemic illness; however, the ASIA criteria utilized to diagnose silicone toxicity are not reliable, and if ASIA becomes the standard by which silicone toxicity is defined it will undoubtedly be negated by future scientific panels.

The following two case histories exemplify the recognition and vindication sought by ailing implant recipients.

Case # One - A 22 y.o.w.f., previously in good health and on no medications, underwent bilateral breast augmentation in 2013 with the insertion of Mentor cohesive silicone gel-filled breast implants. Within two months she began to experience breast pains, chest pain and pressure, fatigue, weakness, and bilaterally enlarged axillary lymph nodes. Over the next three years she developed a multisystem illness encompassing night sweats, metallic taste, headaches, vitiligo on her arms, skin freckling on her arms and anterior chest wall, foul body odor, cognitive dysfunction (memory lapses, poor assimilation of new material, confusion, and problems with name recall and word recall), pain and stiffness in her hands and knees, two hours of morning stiffness, photosensitivity, nail cracking and splitting, two different types of skin rashes on the anterior chest, posterior trunk, shoulders, arms and feet (punctate red pin-head sized papules; also pustules), itching, poor wound healing, bruising, shortness of breath on exertion, dry eyes, abdominal pain, loose stools alternating with constipation, pins and needles and burning pains in her extremities, sore throats, dysphagia, and odor and smell hypersensitivity (with nausea, dizziness, and headaches from cleansers, make-up, perfumes, detergents, room fresheners, deodorants, cigarette smoke, and exhaust fumes). Physical examination was notable for 0mm tear formation on a Schirmer test, 1.5cm bilateral axillary lymph nodes, freckling and pigment changes on the skin (as noted above), tenderness to palpation of multiple anterior ribs, swelling with pain on motion in the PIP joints of her hands, micronodularity of both breasts, two types of skin rashes (as noted above), nail friability, and easy muscle fatigue on repetitive muscle testing. Routine laboratory tests, as well as ANA, were normal or negative. Removal of intact implants and capsulectomies were performed 3 and ½ years after her original surgery. Within seven weeks she began to notice some improvement in her condition, and six months after explantation she has experienced improvement and/or resolution of 80% of her overall symptoms and signs.

Case # Two - A 40 y.o.w.f., previously in good health and on no medications, underwent bilateral breast augmentation in 2012 with the insertion of Mentor cohesive silicone gel-filled breast implants. Within one month she began to experience breast pains, itching, urticaria on her abdominal wall, and red pin-head sized papules on her neck and arms. Over the next four years she developed a multisystem illness encompassing dry eyes and dry mouth, chest pain, bilateral axillary lymphadenopathy, sore throats, recurrent bladder infections, recurrent ear infections, fatigue, muscle weakness, pain and stiffness in her shoulders, hands, wrists, knees, hips, and ankles, one hour morning stiffness, metallic taste, myalgias, abdominal pain, nausea and vomiting, loose stools, night sweats, muscle twitching, cognitive dysfunction (similar to case # one), pins and needles and burning pains in her extremities, blurry vision,
photosensitivity, nail cracking and splitting, headaches, bruising, shortness of breath on exertion, splotchy hyperpigmentation of her face and neck, hypopigmentation on her anterior chest, posterior trunk, shoulders and arms, foul body odor, dysphagia, and odor and smell hypersensitivity (similar to case # one). Physical examination was notable for 0mm tear formation on a Schirmer test, 2cm bilateral axillary lymph nodes, pigment changes on the skin (as noted above), two types of skin rashes (as noted above), tenderness to palpation of multiple anterior ribs, pain on motion of multiple small and large joints, and several ecchymoses. Routine laboratory tests, as well as an ANA were normal or negative. A rheumatologist prescribed NSAID’s, methotrexate, leflunamide, and Enbrel without help. Removal of intact implants and capsulectomies were performed 4 and ½ years after her original surgery. Within four weeks she began to notice some improvement in her condition, and eight months after explantation she has experienced improvement and/or resolution of 90% of her overall symptoms and signs.

Recent publications by University of Oregon researchers have added still another dimension to this saga (24,25). It is alleged that silicone gel can act as a magnet for certain chemicals and toxins that one might encounter in their everyday environment. It is already known that silicones attract estrogen molecules, thereby acting as an independent reservoir to disturb the body’s equilibrium of normally well-controlled hormone levels (12). Silicones are also lipophilic, and they readily adhere to fatty acids and phospholipids (including myelin components) as well as adipocytes (24,25). The chemicals and toxins studied by the Oregon researchers are also lipophilic. Translation: chemicals and toxins are therefore naturally attracted to silicones and visa versa. In addition to heavy metals, numerous chemicals are utilized in the manufacturing processes to synthesize silicone gel (19). Many of these are neurotoxins and carcinogens, and given the recent revelations above they probably do not fall out of the soup mixture at the end. In addition to providing still another mechanism for silicone toxicity, could these phenomena also be related to the recent evidence linking a rare type of cancer, anaplastic large cell lymphoma (ALCL), to certain types of silicone gel-filled breast implants (26)?

Why doesn’t every recipient of silicone gel-filled breast implants become ill? Part of the answer may lie in the human evolutionary process itself. An enzyme, silicase, is normally found in invertebrates such as starfish species, and aids in the degradation and dissolution of silica and other harmful silicon-containing molecules (29). This enzyme activity was lost in higher organisms (12), but perhaps there are some women who still retain the capacity to synthesize it, and thus have the capability to neutralize silicon-containing compounds. If there is a protective lineage, then such recipients would be considered “non-responders,” as opposed to the “over-responders” hypothesized by the ASIA proponents who opine that one’s genetic make-up is a factor producing adverse systemic autoimmune reactions to silicone (5).

So what should we call this new disease entity? ASIA? Human adjuvant disease? Silicone implant incompatibility syndrome? Autoimmune systemic silicone intolerance? Siliconosis? For simplicity we probably should use the phrase “silicone-induced toxicity.” But clearly there is nothing “simplistic” regarding this entity, and scientists with a PhD in biochemistry need to get involved with the research. One thing, however, is now perfectly clear: silicone gel-filled breast
implants cause a distinct and verifiable illness if one utilizes proper methodology to define it (1,4,16,20).

REFERENCES

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