

P E T I T I O N

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ACTION REQUESTED: That the United States Food and Drug Administration issue a warning statement, or cause appropriate parties to issue warning statements, consistent with the known, available science in regard to the safety of medical devices manufactured with silicone which has been catalyzed with hexachloroplatinate.

This warning statement should include at a minimum the following statements (or words to this effect):

(1) In the workplace setting, the medical literature states that no person should come into contact with a liquid or solid containing the chemical catalyst called hexachloroplatinate. Some products sold for human internal and external use contain this catalyst, including silicone gel breast implants, silicone-envelope saline-filled breast implants, certain implanted fluid shunting devices, other implanted devices used in plastic and bone surgery and dermatological-use silicone gel used to help reduce scarring.

(2) Although no large scale human epidemiological studies in regard to platinum-caused disease caused via medical devices have been undertaken, in the workplace setting, persons with evidence of asthma and rhinitis who have been exposed to hexachloroplatinate are considered to have a disease caused by hexachloroplatinate until proven otherwise.

(3) Extremely small amounts of hexachloroplatinate are known to trigger immunologic reactions, cause asthma and damage brain cells, in addition to the other health effects which have been reported in the medical literature.

(4) Although there has been disagreement over the exact type of platinum emitted by silicone gel breast implants, there is no disagreement that hexachloroplatinate is used in their manufacture. Furthermore, there has been no disagreement that even intact breast implants emit some form of platinum.

STATEMENT OF GROUNDS: Attached to this Petition is a document prepared for the United States Federal Court which had contemplated the legal issues invoked by illnesses perceived to be caused by silicone gel breast implants. It sets forth the scientific grounds for the Petitioner's request. It does not include the recently presented work of E. Lykissa, PhD. in which Dr. Lykissa speciated platinum ions liberated from Silicone Gel Breast Implants, providing a basis for even a stronger warning than this Petition requests.

This Attachment was prepared after the Petitioner acting individually notified Judge Pointer of serious factual errors published by his so-called Science Panel in regard to the biological activity of platinum catalyst. Although the Petitioner is unaware of the entire

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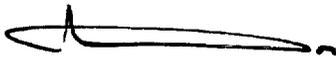
spectrum of ensuing legalities, the Attachment was ultimately prepared for the benefit of the so-called Science Panel at Judge Pointer's initiation.

Based on a review of the published depositions of the so-called Science Panel, it is clear that this document was not read in its totality by the so-called Science Panel. Furthermore, this document was not contemplated by the National Academy of Science Committee assembled in regard to the issue of Silicone Gel Breast Implants. It was completed after the close of its deliberations.

CERTIFICATION: The Attachment includes in it the criticisms raised by the attorneys defending the manufacturers of Silicone Gel Breast Implants, and the science which answers them, providing a concrete grounding for granting of this petition. It is the Petitioner's understanding that a separate document exists which was assembled by these defense attorneys.

The Petitioner does not possess a copy of this document. Although it is the Petitioner's belief that criticisms raised were answered in the Attachment, it is furthermore the Petitioner's belief that it would be much easier for the FDA to get a copy of this document than it is for the Petitioner.

Submitted October 16, 2000.



Michael R. Harbut, MD, MPH
248.559.6663
22255 Greenfield, #440
Southfield, Michigan.

CENTER FOR OCCUPATIONAL & ENVIRONMENTAL MEDICINE, P.C.

22255 GREENFIELD ROAD, SUITE 440
SOUTHFIELD, MICHIGAN 48075
(248) 559-6663
FAX (248) 559-8254

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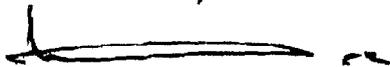
FOOD AND DRUG ADMINISTRATION
DOCKET MANAGEMENT
ATTENTION: JERRY BUTLER
FAX: 301-827-6870

THE FOLLOWING IS AN AMENDMENT TO SUBMITTED PETITION
FOR WARNING LABEL ON SILICONE GEL IMPLANTS WITH
REGARD TO THE ENVIRONMENTAL IMPACT STATEMENT.

"THIS PETITION IS CATEGORICALLY EXEMPT FROM AN
ENVIRONMENTAL IMPACT STUDY."

THANK YOU FOR YOUR ATTENTION IN THIS MATTER.

RESPECTFULLY,



10.23.00

MICHAEL R. HARBUT, MD MPH FCCP

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

IN RE: SILICONE GEL BREAST : Master File No
IMPLANT PRODUCTS LIABILITY : CV 92-P-10000-S
LITIGATION (MDL-926) :

PLAINTIFFS' SUPPLEMENTAL SUBMISSION ON THE CHEMISTRY
AND TOXICOLOGY OF PLATINUM

DATED: March 25, 1999

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I. EXECUTIVE SUMMARY

The Parties agree that “platinum salts” cause both toxicity and systemic hypersensitivity reactions in humans; but the Defendants contend that there are no “platinum salts” in silicone gels and elastomers. The Plaintiffs, in this Submission, prove that platinum salts are in the completed gels and elastomers. The Plaintiffs also prove, especially with genetically susceptible individuals, that both elemental platinum metal and sub-micron sized powders of elemental platinum can also be both toxic and hypersensitizers.

Section II of Plaintiffs’ Supplemental Submission on Platinum identifies the four types of hypersensitivity responses as well as the clinical signs and symptoms associated with each type. This section also reviews the historical “lack of curiosity” of the Defendants in pursuing issues of platinum toxicity and hypersensitivity.

Section III, subsection A establishes that unreduced chloroplatinic acid (platinum salts) remain in all silicone gels and elastomers cured with platinum catalyst. Documents and testimony from the defendants, as well as a patent held by AT&T, prove Plaintiffs’ assertion that platinum salts remain in the completed product, and this is confirmatory of Doctor Lykissa’s positive platinum salts findings, in vitro.

Subsection B establishes that the Defendants knew that soluble platinum (i.e., platinum salts) leaches out of elastomers and gels in water; and they knew this independent of the work of Doctor Lykissa.

Subsection C identifies the role of genetic and species variability and susceptibility in the onset of disease(s) in response to elemental platinum, sub-micron sized elemental platinum powders and to platinum salts.

Subsection D reviews the research in the area of orthopaedic appliances which establishes that elemental platinum metal, as well as other elemental noble metals, can provoke asthma and other hypersensitivity responses in genetically susceptible individuals.

Subsection E demonstrates that the defendant silicone manufacturers knew that platinum salts were especially allergenic in certain animal species and not in others, and this, explains the "false negative" results touted by the Defendants in their Supplemental Submission on Platinum.

Subsection F identifies the important role played by eosinophils as a marker for certain allergic diseases as well as reviewing the Defendants' historic animal research and the eosinophil findings in that research.

Subsection G reviews a comparison of the signs, symptoms and diseases of women with breast implants and their relationship to hypersensitivity and toxic presentations.

Subsection H compares the allergic responses seen in patients receiving platinum chemotherapies with the allergic responses seen in women with silicone gel breast implants; and,

Subsection I rebuts the assertions of the Defendants and shows the significant toxic and hypersensitivity responses to platinum electrodes and solid elastomer shunts and other implantable orthopaedic devices.

Section IV contains the responses of Doctors Templeton, Lykissa and Harbut to the challenges offered by the Defendants in their Supplemental Submission on Platinum.

Dr. Templeton's reply explains his study's methodology and why the Defendants' challenge is wrong on the science. Although his positive platinum findings are adverse to the Defendants' position, the legitimacy of his work stands unchallenged.

Dr. Lykissa's response details his experimental confirmation (in vitro) of the presence of complexed platinum (platinum salts) in the Defendants' gel and elastomer products. His reply also refutes the Defendants' argument that the platinum catalyst conversion process is total and irreversible; and he shows why the resulting platinum residual in Defendants' gels and elastomers is in an ionic, not zero valance state.

Dr. Harbut's reply, and the computation of the amounts of platinum salts (unreduced chloroplatinate) present in two 250 cc silicone gel implants (Computed by Roger Wabeke, MSc, MScChE, CIH, CHMM, PE), demonstrate an in vivo platinum salts exposure to platinum in women with silicone gel implants an amount 1000 x greater than the occupationally allowed limit.

Dr. Harbut's reply refutes the Defendants' challenge to his platinum asthma article published in the peer reviewed Israeli Journal of Occupational Health. Dr. Harbut also identifies the peer reviewed literature establishing the allergenicity and toxicity of elemental platinum, and sub-micron sized elemental platinum powders, as well as platinum salts. Finally, Dr. Harbut presents the Pet Scan reports of two

patients (with implants and after explantation). The abnormal brain findings resolved after explantation.

II. OVERVIEW OF PLATINUM METAL TOXICITY AND HYPERSENSITIVITY

A. Medical Mechanisms of Toxicity and Hypersensitivity

Protein-reactive chemicals, metal salts and drugs, commonly classified as immunological haptens, are major environmental noxes targeted at the immune system of mammals. They may not only interfere with mammalian defense systems by toxicity, but more often by evoking hapten-specific immune responses resulting in allergic and eventually autoimmune responses.¹

The immune status of the individual exposed, is a variable which must be taken into account in any consideration of the factors influencing the metabolism and toxicity of metals.² The commonly occurring phenomena stemming from cellular reactivity to platinum (and other noble metals) can be classified into **four types** of immune response.³

Type I: Anaphylactic of Immediate Hypersensitivity

Under this type, an IgE antibody reacts with the antigen on the surface of mast cells releasing vasoactive amines. Clinical reactions, although varied, may consist of rhinorrhea, conjunctivitis, asthma, urticaria, or systemic anaphylaxis. The cutaneous, mucosal, and bronchial reactions to platinum have been attributed to type I hypersensitivity, although type III reactions may also be involved.

¹ Weltzein, H.Y., Moulon, C., Martin, S., Padovan, E., Hartmann, U., Kohler, J. "T Cell Immune Responses to Haptens. Structural Models for Allergic and Autoimmune Reactions." Toxicology, 107:141-151 (1966) (Exhibit 1, Record No. 7389]

² Kazantzis, G., "The Role of Hypersensitivity and the Immune Response in Influencing Susceptability to Metal Toxicity." Environmental Health Perspectives, 25: 111, 111-118, (1978). [Exhibit 2, Record No. 7390]

Type II: Cytotoxic Hypersensitivity

Type II reactions occur when the humoral antibody, which is an IgG immunoglobulin, reacts with an antigen or hapten bound to the cell surface and fixes complement to produce cell death. Although these reactions occur in a variety of patients, they also can play a part in multi-system hypersensitivity diseases, e.g., SLE.

Type III: Immune Complex Hypersensitivity

Type III reactions occur when an antibody combines with soluble antigen and the complex deposits in tissues, fixing complement and gives rise to a polymorphonuclear inflammatory response. In this type, the clinical outlook is dependent on the relative proportions of antigen and antibody, as well as the genetic sensitivity of the species and individuals within the species (see Section III.C. below). With antibody excess, the complexes are rapidly precipitated, usually close to the site of origin of the antigen, giving rise to an Arthus reaction. This immune complex reaction is also responsible for the systemic reaction known as serum sickness.

Type IV: Cell-Mediated Hypersensitivity

Type IV reactions are also known as delayed-type hypersensitivity. This reaction is mediated by thymus-dependent lymphocytes, taking 24-48 hours to develop in sensitized individuals compared to 15-30 minutes for anaphylactic and 4-8 hours for Arthus reactions. Delayed hypersensitivity can be transferred by the

³ Id.

small number of specifically sensitized small lymphocytes present in a lymphocyte suspension.⁴

The Defendants' Supplemental Submission on Platinum fails to recognize that hypersensitivity is also a toxic reaction. For patients receiving gold salt therapy, for example, skin rash and hypersensitivity are recognized as the most common drug toxic manifestations. This reactivity would be expected for other metal salts, as well.⁵ Kazantzis' states that the clinical effects of metal exposure can be varied, giving rise to conjunctivitis, rhinitis, asthma, urticaria, contact dermatitis, proteinuria, nephrotic syndrome or blood dyscrasia.⁶ Of these effects, cutaneous hypersensitivity is the most common, affecting both industrial and general population groups. Metal compounds used in therapeutics and metals used in orthopedic prostheses have also been responsible for hypersensitive reactions. (See Section III.D. below.)

It should also be recognized that not all platinum toxic effects are distinct clinical manifestations,⁷ but include tinnitus, nausea, vomiting, leucopenia, thrombocytopenia, electrolyte disturbances, seizures and cardiac abnormalities, in addition to the allergic type responses.⁸ Plaintiffs' previous submissions to the 706 Science Panel and the Court identify silica, low molecular weight cyclics and other

⁴ Id.

⁵ Id.

⁶ Id.

⁷ Calabresi, P., Parks, R.E. "Antiproliferative Agents and Drugs used for Immunosuppression." In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The Pharmacological Basis of Therapeutics. New York: Macmillan; 7th ed., 1247-1306 (1985). [Exhibit 3, Record No. 7391]

⁸ Id. [Calabresi]

co-factors acting alone, or in synergy, as being capable of stimulating this type response.

It should be recognized that this submission on platinum does not claim that platinum, or platinum salts alone, are responsible for all clinical manifestations appearing in patients with silicone gels and elastomers. However, as presented below, the peer-reviewed medical and scientific literature supports Plaintiffs' claims that platinum metal, sub-micron elemental platinum particles, platinum colloides and platinum salts, have proved their ability to cause systemic disease in humans (and animals) and are a factor or co-factor of illness in the Plaintiff breast implant population.

B. The Toxicological and Hypersensitivity Research Activities of the Defendants

From the previous submissions of the defendants, as well as their Supplemental Submission on Platinum, the defendants assert that they have done extensive testing on silicone elastomers and gels, looking for both toxic and hypersensitivity responses. The studies and tests they presented Science Panel were carefully selected, but incomplete.

Before beginning the substance of this section, a brief industrial timeline is helpful.

A number of well-respected American corporations have been involved in the manufacture of silicone gels and elastomers for human implantation. During the history of this industry, the most scientific, able and sophisticated of these companies were the first to drop out of the business of manufacturing gels and

elastomers for human implantation. General Electric left the field in 1976; Minnesota Mining and Manufacturing (3M) left the field in 1984; years before the current "breast implant" litigation. Both of these companies, as well as Dow Corning, are responsible for some of the early research on gel and elastomer toxicity and hypersensitivity.

On June 28, 1977, 3M employee Elaine Duncan presented a report to 3M analyzing the several components of silicone gels and elastomers, including a spectrographic analysis of their company's (McGhan) gels and elastomers, as well as the gels and elastomers of some of their competitors.⁹ Although prepared for multiple purposes, this Report found platinum present at 10 parts per million in the elastomer, and .8 parts per million in the gel of Cox-Uphoff. This report also found 8-10 parts per million of platinum in McGhan's elastomer shells.¹⁰

On February 17, 1984, Dow Corning's William Boley wrote a memo criticizing an outside researcher's proposal to study the "immunogenicity of silicone."¹¹

In his critique, Boley suggested that "...history has shown that rarely, if ever, does a patient elicit a 'hyper-response' to silicone. Therefore, it is highly improbable that such a response will occur for evaluation." Of greater interest was

⁹ 3M Report, Duncan to Coyne, June 28, 1977, Bates No. MC8490-8498. [Exhibit 4, Record No. 7392]

¹⁰ Id., Bates No. MC8494. Even though Duncan's test results reported 1-10 parts per million of platinum in gels and elastomers, Defendants' Supplemental Submission on Platinum (at 18) admits to 1-20 parts per million. At pgs. 19-20 of Defendants' Submission they have one elastomer finding of 42 parts per million. This finding is dismissed by the Defendants as a "spurious result." On the contrary, Plaintiffs contend that this alleged "spurious result" is evidence of the great variability in platinum in gels and elastomers, sometimes the result of accident and sometimes the result of intentionally adding more platinum because the reactivity of the platinum catalyst used by the Defendants diminishes with age; and to achieve the same catalytic result, more of the older, weaker catalyst has to be added.

Boley's conclusion that "...The study...will at best create the need for a lot more testing."¹²

A day earlier, Talmage Holmes, the Director of Epidemiology at Dow Corning, wrote to A. H. Rathjen, an executive at Dow Corning, on the subject of the "S. H. Miller study protocol."¹³ In suggesting that Dow Corning should support Dr. Miller's proposed study, Director Holmes expressed concern that "...It seems almost inconceivable that we do not know more about the human immunologic response to silicone...."¹⁴

Three months later, Dow Corning employee, Eldon Frisch, in a memo to William Boley, dated May 9, 1984, informed Boley that Dow Corning's competitor, Baxter, had an interesting poster exhibit at a recent biomaterials meeting which demonstrated a cell culture method developed for the assessment of immunotoxicity.¹⁵ Dow Corning's Frisch went on to report that Baxter has "...tested a number of materials, including silicones, and have found that many, if not most, plastics and elastomers elicit an immunotoxicity reaction."¹⁶ Dow Corning's Frisch went on to suggest that such research might be of interest to Dow

¹¹ Memo, Boley to Cooper, "Comments on Attached Proposal for Study of Immunogenicity of Silicone." Bates No. DCCK MM 205507. [Exhibit 5, Record No. 7393]

¹² Id.

¹³ Memo, Holmes to Rathjen, "S. H. Miller Study Protocol," February 16, 1984. Bates No. DCCK MM 205503. [Exhibit 6, Record No. 7394]

¹⁴ Id.

¹⁵ Memo, Frisch to Boley re "Immunotoxicity Assay Method," May 9, 1984. Bates No. DCCK MM 037828. [Exhibit 7, Record No. 7395].

¹⁶ Id.

Corning because of its relationship to "...the alleged case of human adjuvant disease."¹⁷

The stated objective of the proposed Miller study which Dow Corning did not fund or pursue, was to "...investigate the possibility of humoral or cellular immune hypersensitivity response to one or more antigenic ligands in the Dow Corning 360 fluid."¹⁸

As of this time period in 1984, no one had identified the specific antigenic ligands or gel/elastomer components that might be stimulating immune responses in implant patients. What is clear, however, is that the industry did not want to look for what it might find.

On March 12, 1987, Dow Corning's Eldon Frisch wrote a memo to Dan Hayes, also of Dow Corning.¹⁹ In his memo, Frisch reported on his trip to Wayne State University, School of Medicine, and his meeting with Professor Hegggers. In addition to Hegggers, there were two PhD immunologists and one PhD clinical chemist present. Dow Corning's Frisch reported that, "As a group, they are firmly convinced that some patients develop an immune response to implanted silicone...synovitis with bone and joint implants, infection, 'rejection reactions'"²⁰

Frisch further reported to his colleagues at Dow Corning that the people at Wayne State University "...believed that it would be possible to develop a testing

¹⁷ Id.

¹⁸ Miller proposal. Bates No. DCCK MM 205518. [Exhibit 8, Record No. 7396]

¹⁹ Memo. Frisch to Hayes re Dr. John Hegggers. University Health Center, Wayne State University, March 12, 1987. Bates No. DCC 00M 600239-40. [Exhibit 9, Record No. 7397]

²⁰ Id.

procedure that could be conducted rapidly and inexpensively to pre-test patients to determine which ones had potential for developing such an immune response.”²¹ Dow Corning, for reasons that one can only speculate, chose not to fund Dr. Hegggers’ research (see Section III.(I)(2) below).

As of 1987, the hypersensitizing agent(s) present in gel and elastomer were still not yet specifically identified.

In the mid 1990’s, after several years of manufacturer-financed research on a variety of silicone related subjects, a group of “industry sensitive” researchers out of the University of Toronto, Toronto, Canada, submitted a follow-up grant application to the silicone manufacturers group they had previously served. Their multi-faceted proposal was accepted, solely on the condition, that they not conduct proposed research on the hypersensitizing potential of platinum.²²

In his research proposal, Professor Templeton suggested that “platinum...commonly used as catalyst(s) (sic) in the condensation reactions forming polymeric organosilicones...” and that “If residual catalyst remains...its release as a soluble metal salt would represent a potential immunosensitizing stimulus.”²³ Dr. Templeton’s published research in the area of platinum ended with the publication of his paper “Measurement of Platinum in Biomedical Silicones by

²¹ Id.

²² Templeton, et.al., Grant Application to Study “Elemental Tracers of Breast Implant Rupture, personal communication from Templeton to Peters, dated March 5, 1999. [Exhibit 10, Record No. 7398]

²³ Id.

ICP-MS" in 1995.²⁴ His research on Platinum in gels and elastomers stopped, and the silicone industry continued to fund his colleagues' other directed research.

III. THE SCIENTIFIC FACTS OF PLATINUM: METAL, COLLOIDS, AND SALTS; SILICONE GELS AND ELASTOMERS.

A. Unreduced Chloroplatinic Acid (CPA) is in Most Silicone Gel Implants at the Time of Implant Insertion in Human Patients.

The scientific/chemical thesis of Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum is that the platinum catalyst is 100% unreduced to a colloidal suspension and that the process is irreversible. This is a chemically false premise. In fact, it is axiomatic that no chemical reaction is 100% complete, and no reaction is irreversible. Indeed, even stability, the best that can be hoped for, depends on the chemical law of equilibrium.

Professor Pauling notes that:

"It must be recognized that equilibrium is not a situation in which nothing is happening, but rather a situation in which opposing reactions are taking place at the same rate, so as to result in no over-all change."²⁵

To the extent that variables (e.g., electrical charge, heat, friction, macrophage digestion pressure, etc.) are present, the equilibrium of the reacted state will be predictably disrupted. Once the equilibrium has been disrupted, the reaction may reverse, progress, or otherwise change. This is especially true where the initial reaction was not complete and catalyst (even precursor catalyst) is present.

²⁴ El-Jammal, and Templeton, "Measurement of platinum in biomedical silicones by ICP-MS." Analytical Proceedings Including Analytical Communications, 32:8, 293-295 (1995). [Exhibit 11, Record No. 7399]

Pauling, L. GENERAL CHEMISTRY. Discovery Publishing, Inc., 32:8, 293-295 (1995) [Exhibit 12, Record No. 7399]

Through this submission, the plaintiffs will prove that unreduced platinum salts (PtCl_4 , PtCl_6) are in silicone gel and elastomer implants at the time of human implantation.

The first proof can be found in Defendants' Supplemental Submission on Platinum, pages 38-39, as they try to explain away the very important Dow Corning 1996 guinea pig sensitization study. As the defendants try to explain away this study, they make a crucial admission.

On page 39 of Defendants' Supplemental Submission on Platinum, they state that, "The 1996 guinea pig results are difficult to reconcile...although Platinum #2 may have contained a small amount of unreduced CPA (i.e., chloroplatinic acid)."

This significant admission, which the defendants, in turn, try to explain away, shows that no chemical reaction is complete and that unreduced chloroplatinic acid (CPA) can remain in the implant. It can further be expected that this "unreduced CPA" will continue to have a catalytic, as well as a hypersensitizing effect, on the breast implant recipient who wears this dynamic chemical factory for months, years and even decades.

The second proof that unreduced chloroplatinic acid remains in "completed" gels and elastomers can be found in two articles presented by the Defendants [Record Nos. 8487 and 8491].

The Defendants suggest that the true catalyst is created after all unreduced chloroplatinic acid converts to colloidal form; and this conclusion is based on the research of Lewis and colleagues [Record Nos. 6241 (1986) and 2959 (1991)].

However, when you read the 1997 research of Lewis and colleagues [Record No. 8487] you find that they recognize a problem:

“However, in some cases where silicon-vinyl-containing species were present, the reaction product between platinum and a Si-H-containing compound did not give colloidal platinum species;...” (at pg. 74).

Accordingly, from the 1997 work of Lewis and colleagues we see that the presence of vinyl groups can prevent or block colloid formation.

From Lewis (above), we look next to the Dow Corning Corporation Technical Memo Report presented at Defendants’ Record No. 8491, where we find Dow Corning explaining that, “The elastomer formulation used in the envelope manufacture (i.e., elastomer) consists of a high molecular weight PDMS polymer that contains vinyl functionality. The vinyl groups can either be in the terminal or pendant positions along the polymer chain.”

Accordingly, the Defendants’ own Record references demonstrate a chemical mechanism which explains the presence of unreduced chloroplatinic acid (CPA) in completed elastomers containing vinyl functionalities.

Plaintiffs’ third proof is found in a letter dated January 14, 1977, written by David Sanders, President of Medical Engineering Corporation, a breast implant manufacturer.²⁶

In President Sanders’ letter to doctor Sevinor, responding to specific questions from Sevinor, a Professor from the University of Florida, President Sanders admits that,

"The only residual we know of in the mammary prosthesis is the platinum catalyst..."²⁷

Plaintiffs' fourth proof that active platinum catalyst remains in the completed implant is found in a December 4, 1981, technical report authored by Dow Corning employee Yolanda Peters.²⁸ In her report, Yolanda Peters discusses the problem of elastomers depolymerizing. To explain this phenomena, she writes:

"J. Vallender's report, Dow Corning number 3138, suggested that the reversion is due to incomplete neutralization of the basic catalyst used to make the SiOH end blocked gums."²⁹

Plaintiffs' fifth proof is found in the United States Patent Office. Dr. Wong of AT&T Technologies, Inc., received a patent on May 12, 1987, for a process that Stabilized Silicone Gels.³⁰

In explaining the background of his invention, Dr. Wong reported that in many cases, the silicone polymer was formed by polymerization of a silicone or mixture of silicones in the presence of a platinum catalyst. Further, he reported in many cases it is desired to stop the polymerization process in order to achieve a silicone polymer with a certain gel consistency. He explained that this is true, for example, "...for such things as breast implants...."³¹

Dr. Wong cautions that, "A problem that has been found to exist with such silicones is that, with time, the curing process continues...changing the consistency

²⁶ Letter, David Sanders to Sheldon Sevinor, M.D., January 14, 1977. Bates No. MED0000222435-38. [Exhibit 13, Record No. 7401]

²⁷ Id.

²⁸ Technical Report, No. 127, Y. Peters and C. Hunter, "Feasibility of Fabricating a Mammary Prosthesis with Significant Reduction in Bleed." December 4, 1981. Bates No. M-250086-113. [Exhibit 14, Record No. 7402]

²⁹ Id.

³⁰ United States Patent No. 4,665,148, Wong, May 12, 1987. [Exhibit 15, Record No. 7403]

³¹ Id.

of the silicone from the desired consistency to one that is undesirable." Of course, Dr. Wong's invention was intended to solve the problem of unreduced chloroplatinic acid and the continuing catalytic process.

Plaintiffs' sixth proof is found in the testimony of a defendant silicone scientist, Wilfred Lynch. It should be noted here that Wilfred Lynch is the author of the seminal article "Polymeric Surgical Implant Materials," published in August of 1963.³² Wilfred Lynch is also a scientist/silicone product developer with defendant Surgitek Corporation.

At Professor Lynch's MDL 926 deposition on February 21, 1994, the following questions and the following answers were given:

"Q All right. Now would it be fair to say that this platinum catalyst reaction was used to manufacture all of the gel that was ever used in any MEC breast implant?

A I would expect so.

Q ...the platinum catalyst was used in all of the shell materials that were used on MEC gel breast implants, right?

A Yes. Yes. (Pgs. 114-115)

* * *

Q Mr. Lynch, we were talking before we went off the record a bit about the platinum catalyst. Do you recall that?

A Yes.

Q I think you said that it was actually a platinum salt, right?

A Yes.

³² Lynch, Wilfred. "Polymeric Surgical Implant Materials." MEI000043207. [Exhibit 16, Record No. 7404]

Q All right. What, if anything, did Medical Engineering do at the time it began using that platinum catalyst to determine if that platinum catalyst had any effect on the body?

A We did not do anything about that. (Pgs. 116-117)

* * *

Q Okay, I want to ask a couple of questions about the metallic elements in the gel and the shell material. ...what, if any, metallic elements are in the gel material?

A I don't know of any, unless you're referring to the platinum salt catalyst as a metallic."³³ (Pg. 526)

In conclusion, based on the laws of general chemistry (i.e., no reaction is "complete" or "irreversible"), the admission of the defendants in their "Supplemental Submission," the various defendants' research, Dr. Wong's patent, and the testimony of Wilfred Lynch, only one conclusion can be drawn. The fair scientific conclusion is that unreduced platinum salts remain in, and continue active in, completed implants. This, it should be noted, is consistent with, and supplemental to, Lykissa's finding that platinum salts leach out of silicone gel breast implants.

B. The Defendants Know that Platinum Leaches Out of Silicone Elastomers and Gels in Water.

Aside from the work of Lykissa,³⁴ the defendant implant manufacturers know, or should know, that soluble platinum leaches out of silicone elastomers and gel. They also know, or should know, that this platinum leaches out in a salt form (i.e., chloroplatinic acid).

The work of Potter and colleagues³⁵ establishes that platinum chloride is a water-soluble form of the metal that is used as the preferred catalyst in medical silicone gels and elastomers. Their work further establishes that any soluble platinum leaching from an implant would be expected to distribute in the circulation as a chloroplatinate.

A confirming authority on this question is Dow Corning researcher Robert Parker.³⁶ What did Robert Parker find?

Dow Corning manufactures silicones and elastomers for uses other than silicone gel and elastomer breast implants. They also make silicone "teets." "Teets" are also known as nipples for babies bottles. To determine whether platinum leaches out of the elastomers babies suck on, because The FDA requires that foods coming in contact with elastomers not contain certain levels of contaminants, Dow Corning tested their "teets". In Parker's experiment, tests were run to determine whether organic bound silicon and platinum migrated into the food materials and cow's milk that might come in contact with these "teet" materials. The "teet" materials were exposed to water, ethanol in water, acetic acid and olive oil. Incredibly, the platinum leached out of the "teets" into the water solution,³⁷ as well as each of the other solutions.

³³ Deposition, Wilfred Lynch, Vol. 1, February 21, 1994, 111-117, 526. Analytical Proceedings including Analytical Communications, 32:8, 293-295 (1995). [Exhibit 17, Record No. 7405]

³⁴ Lykissa (1997); Lykissa (1999). [Exhibit 18, Record No. 7406]

³⁵ Potter, M., Morrison, S., Wiener, F., Zhang, X.K., Miller, F.W. "Induction of Plasmacytomas with Silicone Gel in Genetically Susceptible Strains of Mice." Journal of the National Cancer Institute. 86:1058-1065. (1994). [Exhibit 19, Record No. 7407]

³⁶ Dow Corning Technical Report, No. 1990-10000-35570, R. D. Parker, July 23, 1990. Bates No. DCCCK A 022917. [Exhibit 20, Record No. 7408]

³⁷ Id.

As a matter of general chemistry, one would expect that any soluble platinum leaching from a "teet" in water would be leaching out as a water soluble, i.e., as a chloroplatinate, that is, as a platinum salt. Does Dow Corning contend that "platinum metal particles" leach out of its "teets" in water?

C. **The *Platinum* In Silicone Gels and Elastomers Causes Systemic Allergic Responses In Genetically Susceptible Humans.**

Whether *platinum* is in a metal chunk (See Section III.D. below); sub-micron sized particles of elemental platinum, the latter in an alleged colloidal suspension; or a platinum salt, egenetic susceptibility is a prerequisite for systemic allergic response in humans. Further, each of the proceeding forms of *platinum*, although to varying degrees, may cause both toxic and allergic responses in genetically susceptible humans.

1. **There is good evidence that platinum metal, especially sub-micron sized particles of elemental platinum, including particles in colloidal suspension, convert to platinum salts in certain physiologic conditions.**

The internal environment of the human body is corrosive and can oxidize stainless steel orthopedic implants. Voltaric corrosive processes due to ionic exchange in the body are well recognized in orthopaedic surgery. When we consider the sub-micron size of alleged colloidal platinum particles, it is probable they will react within the aggressive chemical milieu of the macrophage phagosome, particularly in the presence of an ongoing tissue response to the biomaterial.³⁸

³⁸ Tang, L., Eaton, J.W., "Inflammatory Responses to Biomaterials." American Journal of Clinical Pathology. 103:466-471. 1995. [Exhibit 21, Record No. 7409]

It is well known that elemental platinum is susceptible to reactions with oxidizing agents. The human body uses agents such as nitric acid (No) within the macrophage phagosome during the natural defense mechanism.³⁹ Accordingly, it would be expected that a certain percentage of platinum particles suspended in the alleged colloidal form would react chemically under such conditions. For this reason, one can expect, even if one accepts the Defendants' argument that elemental platinum is non-toxic and non-allergenic, that a certain portion of the elemental platinum will convert to a salt in the biologic system.

2. **Elemental Platinum Colloid Suspensions, Even Those Not Converting to Salts, Can Be Toxic in the Biologic System**

The dangers of colloidal toxicity were established in the groundbreaking research of Fessenden and Fessenden in 1967.⁴⁰ In their work, Fessenden and Fessenden focused on the toxic dangers of crystalline silica, especially soluble and colloidal forms of silica. As these authors reported:

“Colloidal and soluble silicates...have different biological properties of siliceous dusts. Especially notable is the greater toxicity of the colloidal and soluble forms.”⁴¹

3. **Genetic Susceptibility**

As more fully discussed below (See Section III.E. below), there is ample data to suggest that certain humans and certain species of animals have a genetic susceptibility to hypersensitivity responses to certain challenge agents. It

³⁹ Yoshino, S., “Silicone-Induced Arthritis in Rats and Possible Role for T-Cells.” Immunobiology. 192:40-47. 1994. [Exhibit 22, Record No. 7410]

⁴⁰ Fessenden, R.J., and Fessenden, J.S. “The Biological Properties of Silicon Compounds.” Review Article, ADV Drug Res, 4:95-132 (1967). [Exhibit 23, Record No. 7411]

⁴¹ Id. at 105.

is also known, especially among humans, that the intensity and duration of the challenge, and the response provoked, varies between human individuals. Indeed, as more fully amplified in Section III.E. below, this scientific truth is especially important in determining which animals should be used to test materials for their sensitizing potential.

In concluding this section, the authors have demonstrated that elemental platinum can convert to platinum complexes (i.e., platinum salts); that even colloidal elemental platinum may be dangerous and that the toxic and allergic dangers to humans and animals have genetic variability. Finally, as is demonstrated in the next Section (III.D.), there is good evidence that elemental platinum that has not converted to a salt form or sub-micron particles of metal in colloidal suspension, can be both toxic and allergenic in genetically susceptible humans.

D. **Defendants' Statement that "Platinum Metal is Non-Toxic and Non-Allergenic" is Probably Not True in Susceptible Individuals**

In Williams' textbook on the Biocompatibility of Orthopaedic Implants,⁴²

Williams observes that:

“...almost any metal appears to be potentially able to cause a reaction when introduced into the body, whether as a prosthesis, or in any other form.”⁴³

In an important book published by the United States Department of Commerce in 1981, a ground breaking chapter was written by Drs. Stanley Brown

⁴² Williams, D.F., Biocompatibility of Orthopaedic Implants, 173 (1982). [Exhibit 24, Record No. 7412]

⁴³ Id.

and Katharine Merritt titled "Metal Allergy and Metallurgy".⁴⁴ As an ironic note at this point, it should be reported that one of the editors to this book was Dr. Donald Gibbons, one of the silicone biomaterial scientists in the employ of implant defendant Minnesota Mining & Manufacturing (3M). This publication came out three years before 3M left the silicones for human implantation field.

In their work on metal allergies, Brown and Merritt observe that "Metal allergy reactions result from sensitization of key lymphocytes to metal ion-protein complexes."⁴⁵ These authors, including Katharine Merritt, now Director of Medical Implants at the Food and Drug Administration, predicted that the reactions to implants resulted from the corrosive products (metal ions) complexing with local tissue proteins. From their research they determined that there was a direct correlation between implant degradation and the immune response.⁴⁶ The focus of their research was asthma, caused by elemental metal implants.

From the above evidence we see that elemental platinum, or for that matter any elemental noble metal, can provoke a hypersensitivity response. Whether the elemental metal or the biological system's handling of that metal produces the hypersensitizing complex, is irrelevant to the biologic outcome. That outcome, in genetically sensitive individuals, is a toxic and hypersensitizing response.

⁴⁴ Brown, S., and Merritt, K., "Metal Allergy and Metallurgy," 299-321, Implant Retrieval: Material and Biological Analysis. Conference Proceedings, National Bureau of Standards, LCCCN 80-600194, U.S. Gov. Printing Office (Jan 1981) [Exhibit 25, Record No. 7413]

⁴⁵ Id.

⁴⁶ Id.

From the work of Koch and Baum⁴⁷ we find the report of a patient with contact stomatitis due to combined sensitization to palladium and platinum. Patch testing showed strong and persistent allergic patch test reactions to palladium chloride (1% pet) and ammonium tetrachloro-platinate (0.25% pet) and a weaker reaction to a platinum metal plate.⁴⁸ In orthopedic surgery, this alone would be considered a contra-indication for a prosthetic implant containing reactive metals.⁴⁹

In the work of Koch and Baum we find hypersensitivity responses to the platinum metal plate, as well as to the complexed solutions.

From the materials reviewed in this section, it is probable that Defendants are incorrect when they state that, "platinum metal is non-toxic and non-allergenic."

E. The Silicone Manufacturers Know that Chloroplatinic Acid (CPA) is Especially Allergenic in Certain Animal Species and Not in Others

At pages 36 and 37 of Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum, the defendants mislead the Scientific Panel by stating that "There is no consistent, reproducible evidence of sensitization in animal models."

It has never been the Plaintiffs' contention that there is consistent, reproducible evidence of sensitization in animal models. Indeed, Defendants' slight of hand, misstates the truth—a truth they are well aware of.

⁴⁷ Koch, P., Baum, H.P. "Contact Stomatitis Due to Palladium and Platinum in Dental Alloys." Contact Dermatitis. 34:253-257 (1996). [Exhibit 26, Record No. 7414]

⁴⁸ Id.

⁴⁹ Fisher, A.A. "The Role of Patch Testing in the Management of Dermatitis Caused by Orthopedic Metallic Prosthesis." Cutis. 33:258 (1926). "Patch Testing for Allergic Reactions to Metals in Orthopedic Implants." Cutis. 48:183-184 (1991). [Exhibit 27, Record No. 7415]

Johnson Matthey, an English company, was the main supplier of unreduced chloroplatinic acid (CPA) to Dow Corning Corporation.

Regarding the "sensitization" potential of Dow Corning Platinum No. 2, a Dow Corning memorandum dated June 22, 1983,⁵⁰ reports that:

"Johnson Matthey [supplier of Dow Corning's Platinum No. 2] (sic) indicated that animal toxicity testing for sensitization potential of platinum salts will frequently produce negative results, but that the platinum salts are strong sensitizers to man."⁵¹

The implication that the "false negatives" to Platinum No. 2 sensitization are animal species specific is further reinforced by the work of Schuppe, et. al.,⁵² and Lightfoote⁵³. The ultimate conclusion of these authors is that "differences between various inbred strains of mice revealed that Pt-induced PLN responses are genetically controlled."⁵⁴

It was equally disingenuous of the Defendants to report on Dow Corning's recently completed insult patch studies on Platinum No. 2 (Defendants' Supplemental Submission at 37). Challenging healthy adult human volunteers with Platinum No. 2 does not prove or disprove that Platinum No. 2 can cause sensitization in humans. As Levene reports,⁵⁵ Roberts carried out scratch tests with aqueous solutions of sodium chloroplatinate on sixty platinum workers. His

⁵⁰ Memo A. E. Gamon to P.R. Williams, re "Chloroplatinic Acid/Platinum to Process," June 22, 1983. Bates No. DCCKK A 230413. [Exhibit 28, Record No. 7416]

⁵¹ Id.

⁵² Shuppe, H., Haas-Raida, D., Kulig, J., Bomer, U., Gleichman, E., Kind, P., "T-Cell Dependent Popliteal Lymph Node Reactions to Platinum Compounds in Mice." Int Arch Allergy Immunol, 97:308-314 (1992). [Exhibit 29, Record No. 7417]

⁵³ Lightfoote, M., Bushar, G., Greenweld, W., Langone, J., "Animal Models for Predicting Autoimmune Responses to Bio Materials." (Abstract Center for Devices and Radiological Health, Food & Drug Administration, Rockville, MD). [Exhibit 30, Record No. 7418]

results demonstrated that scratch testing is an unreliable index of liability to develop future symptoms and he claimed that a person with a strong personal or family history of atopic manifestations or of contact dermatitis was more likely to succumb to platinosis than others. Implicitly, this researcher also suggests a genetic predisposition. Such a genetic predisposition would, of course, be consistent with the animal data presented above by Schuppe and Lightfoote.⁵⁶

Supporting and amplifying the opinions presented above is a Dow Corning memorandum, and attached materials, dated August 17, 1983.⁵⁷ In this memorandum, quoting Johnson Matthey representatives, it is noted that:

1. Johnson Matthey feels Pt-Cl compounds are some of the most potent chemical allergens.
2. Pt-(other hallogens) not as potent.⁵⁸
3. One-third of (human, sic) population has allergies. These individuals have a (sic) greater likelihood of Pt-Cl sensitivity; (and there is sic) variability of susceptibility.⁵⁹

In this same Dow Corning memorandum, Johnson Matthey recommends pre-employment testing of potential employees to see if they have general allergies to house mite dust, house dust, ragweed and mixed grass.⁶⁰

This Dow Corning memorandum reporting on Johnson Matthey's knowledge of platinum sensitivity susceptibility is important for a number of reasons. First, it shows that there is a recognized variability of susceptibility. This fact makes

⁵⁴ Id., footnotes 53 and 54.

⁵⁵ Levene, G., "Comment: Platinum Sensitivity." Br. J. Derm. 85:590-93 (1971). [Exhibit 31, Record No. 7419]

⁵⁶ Supra., footnotes 53 and 54.

⁵⁷ Meeting memo and attachments. DCCKK A 230401-415. [Exhibit 32, Record No. 7420]

⁵⁸ Id. at 405.

⁵⁹ Id. at 406.

epidemiological analysis of general populations meaningless. For any epidemiologic study of a human population to be meaningful, the sample and control populations would both have to be matched for general allergy susceptibility. No epidemiologic study done to date has recognized this variability of susceptibility. Second, because one-third of the population has allergies, we would expect that only one-third of the silicone gel breast implant population would have a susceptibility to platinum hypersensitivity. This percentage of reduction further amplifies the difficulty of meaningful epidemiologic sampling where general allergy susceptibility is not controlled.

On page 18 of Defendants' Supplement Submission on Platinum, they use the work of Lewis and colleagues to explain the color formations that occur in silicone gel breast implants. In the Dow Corning memo referenced above, darkened color formations are explained by Johnson Matthey:

"Platinum contamination will be shown by black discoloration on surfaces. Contamination is a real problem."⁶¹

Defendants' Supplemental Submission on Platinum reports, at page 36, that "...there is no consistent, Reproducible Evidence (of) Sensitization in Animal Models."

From the Dow Corning memo referenced above, we find that:

"Johnson Matthey indicated that animal toxicity testing for sensitivity potential of platinum salts will frequently produce negative results..."⁶²

⁶⁰ Id.

⁶¹ Id. at 412.

⁶² Id. at 413.

Based on the totality of evidence presented by the animal researchers in this section (Shuppe and Lightfoote), and the contents of the Dow Corning-Johnson Matthey memoranda of August 17, 1983, we can understand that there would be no consistent, reproducible evidence of sensitization in animal models because of species variation. Indeed, in the next section, the 1996 guinea pig study that so troubles the Defendants, as well as other Dow Corning research, are discussed. In the next section, we also look at eosinophils.

F. Long-Term Implantation of Silicone Gel or Elastomer Increases Eosinophil Levels in Sensitive Animal Species and Sensitive Humans

Casarett and Doull advise that eosinophilia is a marker for certain allergic diseases.⁶³

The Defendants' Supplemental Submission on Platinum recognizes the significance of increased eosinophil levels and misleadingly reports that the National Toxicology Program "looked for, but did not find, any increase in eosinophil levels from long-term implantation of silicone gel or elastomer in female mice."⁶⁴

It is interesting to note that the Defendants offer no discussion of species susceptibility or variability in response to chloroplatinic acid (CPA) challenges. It is also interesting that they did not report Dow Corning's 90-day implant test (M8337-N) where Dow Corning found, in its test animals, "...an increase of eosinophils...at...gel implant sites."⁶⁵

⁶³ Klaassen, C., Casarett & Doull's Toxicology, 5th Ed, at 338 (1996). [Exhibit 33, Record No. 7421]

⁶⁴ Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum, at 34.

⁶⁵ Dow Corning implant test (M8337-N) as referenced in Dow Corning Corporation Toxicology Study, Series No. 10005-1987, by M. Bejarno, August 8, 1985. Bates No. T-031514-1571. [Exhibit 34, Record No. 7422]

As a follow up study on the positive eosinophil finding from implant tests (M8337-9), Dow Corning conducted a 30-day gel implant test on New Zealand White (NZW) rabbits. In this test, Dow implanted gel materials into the paravertebral muscle and ventral subdermal area of male (NZW) rabbits.

This 30-day test on rabbits reached a similar finding to the previous 90-day implant test (M8337-N). The second rabbit test confirmed:

"The presence of eosinophils at the Q7-2218 Gel implant site (which sic) suggests the possibility of immunological sensitization to a compoent(s) of the gel formulation."⁶⁶

Dow Corning employee William Boley determined at this time, August 7, 1985, that "...additional studies are required to either substantiate or disprove the possible sensitization potential of this silicone gel."⁶⁷

From the materials produced by the defendants, it does not appear that follow-up long-term gel implant testing to determine the immunological sensitization risks were conducted on sensitive species until Dow Corning conducted its guinea pig testing in 1996.

On February 3 and February 6, 1995, Dow Corning Corporation took the deposition of treating physician, Dr. Michael Harbut, in the case of Ingoglia v Dow Corning Corporation. At this deposition, Dr. Harbut enunciated the toxic and hypersensitivity dangers of unreduced chloroplatinic acid (CPA).

⁶⁶ Id., at T-031518.

⁶⁷ Id.

On October 30, 1996, Dow Corning completed its study titled, "Skin Sensitization Study of Dow Corning 3-8015 Intermediate (Platinum No. 2) Using the Guinea Pig Maximization Test (GPMT)."⁶⁸

This 1996 study funded by the Dow Corning Corporation, after Dr. Harbut's testimony in the case of Ingoglia, using the latest and most sophisticated testing techniques and controls of an outside lab, found that: "All of the positive control animals exhibited a positive (allergic sic) response...."⁶⁹ Further, in reporting on the "skin effects," the researchers found that: "All of the positive control animals exhibited a positive response at the...challenge site, resulting in incidents and severity indices of 100%...at the 48-hour scoring interval period."⁷⁰

Finally, the researchers of this 1996 Dow Corning guinea pig study, in their introduction, state that: "Dermal application of the test substance corresponds to a potential root of human exposure."⁷¹

If, as the Defendants suggest in their Supplemental Submission on Platinum, the positive results found on the 1996 guinea pig study may have resulted from a "...small amount of unreduced CPA"⁷² they have only themselves to blame. As is noted in the 1996 guinea pig study: "All chemical analyses and attendant

⁶⁸ Dow Corning Report No. 1996-10000-42261, "Skin Sensitization Study of Dow Corning 3-8015 Intermediate (Platinum No. 2) Using the Guinea Pig Maximization Test (GPMT), October 30, 1996. Bates No. DCC838-410001-26. [Exhibit 35, Record No. 7423]

⁶⁹ Id. at DCC838-410003.

⁷⁰ Id. at DCC838-410012.

⁷¹ Id. at DCC838-410008.

⁷² Defendants' Submission at 39.

documentation pertaining to the characterization of the bulk test substance [was] (sic) the responsibility of the Sponsor.”⁷³

The special relationship between gels, elastomers and eosinophils was first observed in the peer reviewed literature in 1978.⁷⁴

Hausner and Schoen were the first to recognize the relationship between silicone gels and eosinophils. In their paper, on pathology, the authors found remote silicone gel in two axillary lymph nodes. They found that these two lymph nodes contained many multinucleated giant cells, and the latter had uniformly distributed nuclei with abundant eosinophilic cytoplasm...⁷⁵

In 1991, Picha and Goldstein published an identical finding in the same journal.⁷⁶

In a histological analysis of the fibrous capsule forming around silicone elastomer implant material “...a variable number of mast cells and eosinophils” were found.⁷⁷

In their conclusion, Picha and Goldstein preescently observed that:

“...we have shown that chemical components used in the manufacture of a silicone implant, when considered individually or as an extract, are not inert, as reflected...by the...granulomatous response and induction of cells derived from the immune system. Transferring these results to the clinical situation suggests that the human response to a gel

⁷³ Supra. footnote 70 at DCC838-410008.

⁷⁴ Hausner, R., Schoen, F., and Pierson, K., “Foreign Body Reaction to Silicone Gel in Axillary Lymph Nodes after an Augmentation Mammoplasty.” Plastic & Reconstructive Surgery, 62(3), 381-384. [Exhibit 36. Record No. 7424]

⁷⁵ Id. at 382.

⁷⁶ Picha, G. and Goldstein, J., “Analysis of the Soft Tissue Response to Components Used in the Manufacture of Breast Implants: Rat Animal Model,” Plastic & Reconstructive Surgery, 87:3. 490-500 (March 1991) [Exhibit 37. Record No. 7425]

⁷⁷ Id. at 493.

prosthesis will vary with respect to the particular implant design, the extent of silicone bleed, the polymeric composition, the mechanical forces within the site, and the individual's immune system.”⁷⁸

G. Breast Implant Women Present With Signs and Symptoms of Platinum and Platinum Salts Toxicity and Allergy, as Reported in the Peer Reviewed Medical Literature.

As Defendants correctly note in their Supplement Submission on Platinum, “One of the principle features of platinum-salt allergy is asthma....”⁷⁹ Such asthmas are documented in the peer reviewed publication by Harbut, published in the Israeli Journal Occupational Health.⁸⁰ And, although the Defendant manufacturers do not like this article, and although the Defendants criticize this article, their criticisms, especially those pertaining to the criteria sets used in evaluating the article, are without basis as is more fully explained in Dr. Harbut’s Reply (See Section IV.C. below). Brown and Merritt also found metals induce asthma, see footnote 44 supra.

From the early work of Bridges, et.al., we find, contrary to the Defendants’ assertion, silicone gel breast implant women present with numerous clinical signs, symptoms and complaints associated with allergic responses. These include in order of incidence, fatigue (a non-specific condition frequently associated with impaired oxygen exchange ability), sicca symptoms (dry eyes, mouth, joint inflammation, etc.), mental confusion (neurotoxicity/CNS involvement), pulmonary symptoms (cough, shortness of breath, dyspnea on exertion, pleuritic chest pain,

⁷⁸ Id., at 499.

⁷⁹ Defendants’ Supplemental Submission on the Chemistry and Toxicology of Platinum, 32.

For a clinical report and opinion on patient Jane Doe see letter of Dr. Harbut.⁸²

Finally, Defendants' Supplemental Submission on Platinum claims that "...There are no controlled...epidemiological studies demonstrating a risk of anything resembling platinum-salt allergy in breast implant recipients."⁸³ The Defendants' statement is true, but misleading.

The defendants' statement that there are no controlled epidemiological studies demonstrating a risk of allergy (hypersensitivity) related to breast implants is true, because no one has looked. There are no studies that have looked and failed to find an association. On this point, the sworn affidavit of Talmage Holmes, PhD, former Director of Epidemiology for the Dow Corning Company between 1984 and 1988, states that as of January 14, 1997, he had reviewed all published epidemiologic studies, including the study of Wells, et.al. (upon which Defendants heavily rely). In his affidavit, Dr. Holmes states, under oath:

"That none of these epidemiologic studies (including Wells') (sic) investigate or assess in any fashion the question of whether breast implants cause allergy or hypersensitivity reactions in breast implant users."⁸⁴

In conclusion, from the early work of Bridges, et.al., (1993) to the current work of Harbut (1999), there is compelling proof that breast implant women present with signs, symptoms and disease consistent with platinum and platinum

⁸² Personal communication, Harbut to Peters, dated March 15, 1999. [Exhibit 40, Record No. 7428]

⁸³ Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum at 31.

⁸⁴ Affidavit Helmich M. Holmes, PhD, January 14, 1997, and exhibit listing the 10 epidemiologic studies upon which his affidavit is based. [Exhibit 41, Record No. 7429]

salts' toxicity and allergy, as reported in the non-epidemiologic peer reviewed medical literature. Further, based on the affidavit of the former Director of Epidemiology of the Dow Corning Corporation, there is ample evidence that the epidemiologic studies cited by the defendants (including the work of Wells, et.al.), are without value or use on this question.

H. The Pattern of Allergic Responses Seen in Women With Silicone Gel Breast Implants Has Also Been Reported in Cancer Patients Receiving Platinum Compounds, Contrary to the Assertions of the Defendants.

The Defendants' Supplemental Submission on Platinum states that "Platinum-Containing Drug Toxicities Are Not Manifested In Women With Silicone Breast Implants."⁸⁵ But women receiving platinum containing cancer drugs present with allergic responses similar to those experienced by women with silicone gel and elastomer implants.

Pre-clinical data suggests that ormaplatin (tetrachloro-(dl-trans)-1 2-diammino-cyclohexaneplatinum) has substantial pharmacologic activity.⁸⁶ Clinical development of ormaplatin, however, was terminated due to increased frequency of neurological complications noted over other platinum agents. However, the pharmacokinetics are, in general, similar to those of other clinically used platinum compounds.

⁸⁵ Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum at 39.

⁸⁶ Figg, W.D., Christian, M.C., Lush, R., et al., "Pharmacokinetics of Elemental Platinum (ultrafiltrate and total) After a Thirty Minute Intravenous Infusion of Ormaplatin." *Biopharm. Drug Dispos.* 18:347-359 (1997). [Exhibit 42, Record No. 7430]

or abnormal pulmonary function test results), alopecia (may be an immune mediated condition), and rash.⁸¹

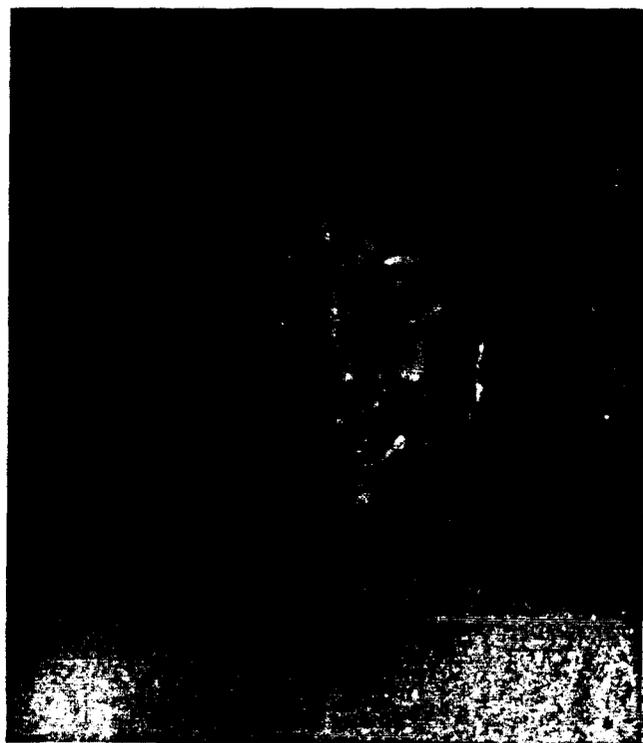
Although there are dangers with individual case reports, the following case report is instructive. The following individual, Jane Doe, was a fashion model prior to silicone gel breast implantation. After breast implantation, she developed a body-wide rash, especially prominent on the face (see figure 1). This rash continued during Jane Doe's period of implantation and failed to respond to any treatment. After explantation, the rash completely resolved (see figure 2).

Figure 1



With Implants

Figure 2



After Explantation

⁸⁰ Harbut, M. and Churchill, B., "Ásthma in Patients With Silicone Breast Implants: Report of a case series and identification of hexachloroplatinate contaminant as a possible etiologic agent," Israeli Journal of Occupational Health, 3(1):73-82 (1999). [Exhibit 38, Record No. 7426]

⁸¹ Bridges, A., Conley, C., Wang, G., Burns, D., and Vasey, F., "A Clinical and Immunologic Evaluation of Women With Silicone Breast Implants and Symptoms of Rheumatic Disease," Annals of Internal Medicine, 18:12, 929-936 (June 1993). [Exhibit 39, Record No. 7427]

For a clinical report and opinion on patient Jane Doe see letter of Dr. Harbut.⁸²

Finally, Defendants' Supplemental Submission on Platinum claims that "...There are no controlled...epidemiological studies demonstrating a risk of anything resembling platinum-salt allergy in breast implant recipients."⁸³ The Defendants' statement is true, but misleading.

The defendants' statement that there are no controlled epidemiological studies demonstrating a risk of allergy (hypersensitivity) related to breast implants is true, because no one has looked. There are no studies that have looked and failed to find an association. On this point, the sworn affidavit of Talmage Holmes, PhD, former Director of Epidemiology for the Dow Corning Company between 1984 and 1988, states that as of January 14, 1997, he had reviewed all published epidemiologic studies, including the study of Wells, et.al. (upon which Defendants heavily rely). In his affidavit, Dr. Holmes states, under oath:

"That none of these epidemiologic studies (including Wells') (sic) investigate or assess in any fashion the question of whether breast implants cause allergy or hypersensitivity reactions in breast implant users."⁸⁴

In conclusion, from the early work of Bridges, et.al., (1993) to the current work of Harbut (1999), there is compelling proof that breast implant women present with signs, symptoms and disease consistent with platinum and platinum

⁸² Personal communication, Harbut to Peters, dated March 15, 1999. [Exhibit 40, Record No. 7428]

⁸³ Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum at 31.

⁸⁴ Affidavit Helmich M. Holmes, PhD, January 14, 1997, and exhibit listing the 10 epidemiologic studies upon which his affidavit is based. [Exhibit 41, Record No. 7429]

salts' toxicity and allergy, as reported in the non-epidemiologic peer reviewed medical literature. Further, based on the affidavit of the former Director of Epidemiology of the Dow Corning Corporation, there is ample evidence that the epidemiologic studies cited by the defendants (including the work of Wells, et.al.), are without value or use on this question.

H. **The Pattern of Allergic Responses Seen in Women With Silicone Gel Breast Implants Has Also Been Reported in Cancer Patients Receiving Platinum Compounds, Contrary to the Assertions of the Defendants.**

The Defendants' Supplemental Submission on Platinum states that "Platinum-Containing Drug Toxicities Are Not Manifested In Women With Silicone Breast Implants."⁸⁵ But women receiving platinum containing cancer drugs present with allergic responses similar to those experienced by women with silicone gel and elastomer implants.

Pre-clinical data suggests that ormaplatin (tetrachloro-(dl-trans)-1 2-diammino-cyclohexaneplatinum) has substantial pharmacologic activity.⁸⁶ Clinical development of ormaplatin, however, was terminated due to increased frequency of neurological complications noted over other platinum agents. However, the pharmacokinetics are, in general, similar to those of other clinically used platinum compounds.

⁸⁵ Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum at 39.

⁸⁶ Figg, W.D., Christian, M.C., Lush, R., et al., "Pharmacokinetics of Elemental Platinum (ultrafiltrate and total) After a Thirty Minute Intravenous Infusion of Ormaplatin." *Biopharm. Drug Dispos.* 18:347-359 (1997). [Exhibit 42, Record No. 7430]

Planner, et.al., observed anaphylactic (allergic) reactions to carboplatin in patients receiving that drug for ovarian adenocarcinoma.⁸⁷

Planner, et.al., also report that Cisplatin hypersensitivity has been reported to occur in 1-20% of recipients.⁸⁸ These authors conclude their Comment by stating that, "The risk of carboplatin hypersensitivity should be considered in all patients receiving this therapy...."⁸⁹

In additional case reports by Tonkin, et.al., the authors note that patients suffering hypersensitivity reactions to carboplatin develop tightness around the throat, felt flushed and developed a generalized erythema rash. The rash is described as "widespread" and the patients also developed "chest pain" as part of the reaction.⁹⁰

Incredibly, in their analysis of carboplatin hypersensitivity, Tonkin, et.al., report that:

"It is established that complex salts of platinum are highly allergenic in industry where a number of workers have reported immediate hypersensitivity reactions and allergic asthma."⁹¹

The well published reports of hypersensitivity disorders directly related to platinum containing drugs challenge the Defendants' credibility on the alleged dissimilarity between these two patient populations.

⁸⁷ Planner, R., Weerasiri, T., Timmins, D., Grant, P., Correspondence "Hypersensitivity Reactions to Carboplatin." Journal of the National Cancer Institute, 83:23, 1763-1764 (December 1991) [Exhibit 43, Record No. 7431]; Weiss, R., Bruno, S., "Hypersensitivity Reactions to Cancer Chemotherapeutic Agents," Ann.Internal Med. 94:66-72 (1981); Weiss, R., "Hypersensitivity Reaction to Cancer Chemotherapy," Sem. Oncol, 9:5-13 (1982). [Exhibit 44, Record No. 7432]

⁸⁸ Id. at 1764.

⁸⁹ Id.

⁹⁰ Tonkin, K., Rubin, P., and Levin, L., "Carboplatin Hypersensitivity: Case Reports and Review of the Literature." Eur.J.Cancer, 29A:1356-1357 (1993). [Exhibit 45, Record No. 7433]

I. Defendants' Representation That Elastomer Shunts and Platinum Electrodes Have Been Safely Used Without Allergic Complications in Humans is False, and further, the Peer Reviewed Medical Literature Demonstrates That:

- Elemental platinum electrodes dissolve in the human brain, forming platinum salts; and,
- That silicone elastomer shunts provoke systemic allergic responses in genetically susceptible humans.

1. THE PROBLEM WITH PLATINUM ELECTRODES

In Defendants' Supplemental Submission on Platinum (pg. 28), the Defendants state that "Pure platinum metal is commonly used as a long-term implantable electrode material for cortical stimulation." The implication of the Defendants' statement is that this has been done safely and without systemic allergic complications. This is not true.

In 1965, Rosenberg and colleagues⁹² observed growth inhibition of E. Coli on agar gels in contact with platinum electrodes conducting low voltage current. This observation, that platinum metal converted easily to a biologically active salt,⁹³ led to the discovery of cis-platin,⁹⁴ a pharmaceutical drug currently manufactured and marketed by one of the defendants in this case, Bristol Myers Squibb. The work of Rosenberg and colleagues also demonstrates the relative ease with which elemental platinum converts to an ionic form.

⁹¹ Id.

⁹² Rosenberg, B., VanCamp, L., Grimley, E.B., Thomson, J.J., "The Inhibition of Growth or Cell Division in Escherichia Coli by Different Ionic Species of Platinum (IV) Complexes." J.Biol.Chem 242:1347-1352 (1967). [Exhibit 46, Record No. 7434]

⁹³ Rosenberg, B., Renshaw, E., Van Camp, L., Hartwick, J., Drobnik, J. "Platinum-induced Filamentous Growth in Escherichia Coli." J. Bacteriol. 93:2, 716-721 (1967) [Exhibit 47, Record No. 7435]

⁹⁴ Rosenberg, B., VanCamp, L., Trosko, J.E., Mansour, V.H., "Platinum Compounds: A New Class of Potent Antitumor Agents." Nature. 222:385-386 (1969). [Exhibit 48, Record No. 7436]

The ease with which elemental platinum converts to an ionic form poses a considerable problem in the use of implanted electrodes, as this elemental metal corrodes within the body.⁹⁵ And, as we know, once in an ionic form, Pt⁺ readily binds to plasma proteins and behaves as a hapten in allergic sensitization.

In 1977, Agnew and colleagues⁹⁶ initiated a study to assess the role platinum electrode erosion products played in neuro damage following electrical stimulation of the brain, specifically to distinguish morphological changes resulting directly from electrode solubilization, as opposed to electrical factors.

The first observation of Agnew and colleagues was that the platinum salts generated by the dissolving platinum electrodes produced multiple nucleoli, calcium crystal deposition, abundant intracellular lipids, and preferential neuronal sensitivity.

Histologic examination demonstrated the occurrence MCB and zebra bodies as is found in diseases of known enzyme deficiency, e.g. Hexosaminidase-A deficiency in Tay-Sachs Disease. These findings caused the authors to conclude that, "The presence of these abnormalities in some cells whose morphology (including mitochondria) is otherwise normal, favors a direct intracellular action of

⁹⁵ Black, R.C., Hannaker, P., "Dissolution of Smooth Platinum Electrodes in Biological Fluids, " Appl. Neurophysiol. 42:366-374 (1979); Brummer, S.B., McHardy, J., Turner, J.J., "Electrical Stimulation with Pt Electrodes: Trace Analysis for Dissolved Platinum and Other Dissolved Electrochemical Products," Brain Behav. Evol., 14:10-22 (1977); Brummer, S.B., Robblee, L.S., Hambrecht, F.T., "Criteria for Selecting Electrodes for Electrical Stimulation: Theoretical and Practical Considerations," Ann. N.Y. Acad. Sci. 405:159-171 (1983)[Exhibit 49, Record No. 7437]

⁹⁶ Agnew, W., Yuen, T., Pudenz, R., and Bullara, L., "Neuropathological Effects of Intracranial Platinum Salt Injections," Journal of Neuropathology & Experimental Neurology, 36(3), 533-46 (May 1977). [Exhibit 50, Record No. 7438]

platinum rather than changes secondary to anoxia or microcirculatory disturbance.⁹⁷”

Rosenberg and colleagues, in supporting their analysis, report that salts of platinum, like those of other heavy metals, are toxic and may be expected to act as metabolic inhibitors.

Confirming the work of Agnew and associates, Black and Hannaker⁹⁸ found that in biologic fluids the “. . .corrosion (dissolution) of platinum from smooth platinum electrodes was found to be significant.” Ultimately, these researches concluded that: “The results of these studies suggest caution in the general use of smooth platinum as a chronic implant electrode material.”

2. SILICONE ELASTOMER SHUNTS PROVOKE SYSTEMIC ALLERGIC RESPONSES IN GENETICALLY SUSCEPTIBLE HUMANS

The Defendants’ Supplemental Submission on Platinum states that “The experimental and clinical toxicology of long-term implantable silicone gels and elastomers fails to demonstrate and allergy or systemic toxicity of the type seen from exposure to platinum salts” (Defendants’ Supplemental Submission at 4).

This is not true.

Do you remember Dr. Hegggers, the Wayne State University, School of Medicine Professor, visited by Dow Corning’s Eldon Frisch (See this Submission, at pg. 10.

⁹⁷ Id. at 544.

⁹⁸ Black, R., and Hannaker, P., “Dissolution of Smooth Platinum Electrodes in Biological Fluids.” Appl. Neurophysiol. 42:366-374 (1980). [Exhibit 51. Record No. 7439]

In 1983, Heggors and colleagues studied the phenomena of cerebrospinal fluid shunt failures. Their peer reviewed article concluded that “. . .some of the failures of the hydrocephalus shunts represent an immunologically directed host response evoked, in part, by the silicon in the shunt; i.e., there exists a hypersensitivity to the silicone hydrocephalus shunt.”⁹⁹

In 1988, Kennedy and Singer¹⁰⁰ observed, what was at the time, the unusual finding of eosinophilia in the cerebral spinal fluid of a symptomatic child several years after placement of a silastic ventriculoperitoneal (V/P) shunt.

On CT scan examination, enlarged lateral and third ventricles, a cyst in the right frontal lobe and some generalized cortical atrophy was noted.

In their Discussion, Kennedy and Singer¹⁰¹ concluded that the case demonstrated “. . .a cause-and-effect relationship between the presence of a silastic V/P shunt and the development of a sterile inflammatory reaction. . . and that an erythema (rash) on the skin covering the shunt, was accompanied by a finding of CSF eosinophilia restricted to ventricular (not lumbar) CSF. Further, repeated laboratory investigation showed no evidence of an infectious etiology. Indeed, the persistent symptoms and signs resolved only when the shunt was removed.”¹⁰²

In 1988, Traynelis and colleagues¹⁰³ reported on two cases of CSF eosinophilia occurring concurrently with sterile shunt malfunction. Although they

⁹⁹ Id. at 367.

¹⁰⁰ Kossovsky, N., Heggors, J., Dujovny, D., Diaz, F., and Ausman, J., “Ventricular Shunt Failure: Evidence of Immunologic Sensitization,” Surgical Forum, 34:527-529 (1983). [Exhibit 52, Record No. 7440]

¹⁰¹ Kennedy, C., and Singer, H., “Eosinophilia of the Cerebrospinal Fluid: Late Reaction to a Silastic Shunt,” Developmental Medicine Child Neurology, 30:378-390 (1988) [Exhibit 53, Record No. 7441]

¹⁰² Id. at 388.

weren't sure what was causing the allergic response, they were confident that the shunt failure was the result of an allergic reaction.

In their discussion, Traynelis and colleagues observed that silicone othroplasty has been associated with a severe inflammatory response and eosinophils have also been found in material adjacent to implanted silicone elastomer durral substitutes. They stated that this represented a delayed hypersensitivity reaction to the silicone rubber.

In 1994, Jimenez and colleagues¹⁰⁴ reported on a series of patients who suffered recurrent skin breakdowns over their shunt tracts, although on examination of tissues and fluids, no infections could be found. Indeed, successful resolution of the symptoms only occurred after the silicone shunt material was removed.

In 1995, Hunsaker and Martin¹⁰⁵ described an allergic reaction to a solid silicone implant in medial thyroplasty. These authors, like the researchers before them, noted that "The skin reactions and laryngeal symptoms cleared after removal of the silicone implant."¹⁰⁶

In concluding this section, it is important to recall the eosinophilic findings of Dow Corning researchers in the 1985 rabbit and 1996 guinea pig studies performed by Dow Corning (See Section III.F., pgs. 27-30). It is also important to

¹⁰³ Traynelis, V., Powell, R., Koss, W., Schochet, S., and Kaufman, H., "Cerebrospinal Fluid Eosinophilia Shunt Malfunction," Neurosurgery, 23:5, 645-649 (1988) [Exhibit 54, Record No. 7442]

¹⁰⁴ Jiminez, D., Keating, R., Goodrich, J., "Silicone Allergy in Ventriculoperitoneal Shunts," Child's Nerv. Syst., 10:59-63 (1994). [Exhibit 55, Record No. 7443]

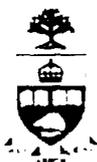
¹⁰⁵ Hunsaker, D., and Martin, P., "Allergic Reaction to Solid Silicone Implant in Medial Thyroplasty," Otolaryngology—Head and Neck Surgery, 113:6, 782-784 (1995) [Exhibit 56, Record No. 7444]

¹⁰⁶ Id. at 783.

recognize that none of the non-Dow Corning researchers referenced in this section were aware that platinum salts, sub-micron elemental platinum particles or other platinum compounds were present in the silicone elastomers that produced the hypersensitivity responses they were observing in their patients and in their studies.

IV. Responses of Drs. Templeton, Lykissa and Harbut to Defendant Manufacturer's Supplemental Submission on the Chemistry and Toxicology of Platinum.

A. DR. TEMPLETON'S REPLY



Department of Laboratory Medicine and Pathobiology

University of Toronto
100 College St., Toronto, M5G 1L5, Canada



Mr. Doug Peters
Charfoos and Christensen
5510 Woodward Ave.
Detroit, MI 48202
USA

March 12, 1999

Fax 313-875-8522

Dear Mr. Peters:

The following are my comments on the discussion of the paper by Dr. El Jammal and myself in the Defendants' Supplemental Submission on the Chemistry and Toxicology of Platinum, dated March 3, 1999.

The Submission states that "After heating silicone gel for 18 h ... The recovery experiments show that recovery of platinum was less reliable at the low end of the detection limit, 1 ppm ($76 \pm 18\%$) as compared to the recovery with higher additions of platinum at 10 ppm ($96 \pm 17\%$)." These numbers do not refer to silicone gel. Rather, under the heading "Silicone oils" we state that "The recovery of Pt added to the diluted sample was ($76 \pm 18\%$) at $1 \mu\text{g l}^{-1}$ and ($96 \pm 17\%$) at $10 \mu\text{g l}^{-1}$. Addition of 1 mg l^{-1} to the original oil gave a recovery of ($112 \pm 9\%$)." This refers to the oil prior to addition of catalyst and polymerization, as is clear in our paper.

The recovery from silicone gel under the refined conditions used for the analyses upon which we based our reported value of 4.5 ppm Pt in the gel is given in Table 1 of our paper (1992, 5.2)

It is also incorrect to state that a recovery of $76 \pm 18\%$ (*sic*) is "less reliable" than a recovery of $96 \pm 17\%$. The values are not significantly different statistically and the variances are comparable.

The Submission states "This experiment also clarified that there are matrix factors, which can artificially elevate the results of the ICP-MS analysis of platinum". I am puzzled why recoveries of *less than 100%* of an added known amount of Pt would be taken as demonstrating that the results are artificially *increased*. Nevertheless, recovery of Pt from the gel was $(99.2 \pm 5.2)\%$, indicating the absence of matrix effects that would either increase or decrease the results.

The Submission states that "The platinum concentrations given for the blanks in Table 1 of the article, along with the standard deviations in the actual platinum measurements, make it clear that 4.0 to 4.5 μg of platinum per gram of gel is an upper limit estimate and may be considered within the range of 1.0 to 2.0 ppm." This is mystifying.

The mean \pm s.d. of the five measurements in aqua regia given in Table 1 is 4.71 ± 0.30 . We do not say that Pt is in the range 4.0 - 4.5 $\mu\text{g/g}$, but rather that it is approximately 4.5 $\mu\text{g/g}$. The average s.d. on the individual measurements is 11% of the individual value. We state that the value of 4.5 $\mu\text{g/g}$ is "several orders of magnitude above the method blank for the procedures". The calculation is as follows, from line 3 of Table 1: 4.39 mg/kg in 1.2 g of gel is 5.27 μg of Pt. This was analyzed in 2.00 ml (footnote * to the Table), so the Pt concentration was $5.27 \times (1000/2) = 2635 \mu\text{g/L}$. The corresponding method blank was 0.83 $\mu\text{g/L}$. In summary, our recovery is $(99 \pm 5)\%$, there is no elevating matrix effect, the analytical imprecision is less than 10% of the measured value, and the blank contributes less than one part in 3000. The Pt content of the gel is $4.71 \pm 0.30 \mu\text{g/g}$, or "approximately 4.5 $\mu\text{g/g}$ " and definitely not "within the range of 1.0 to 2.0 ppm".

Sincerely,



Doug Templeton, PhD, MD
Professor

B. DR. LYKISSA'S REPLY



**BAYLOR
COLLEGE OF
MEDICINE**

One Baylor Plaza
Houston, Texas 77030-3498

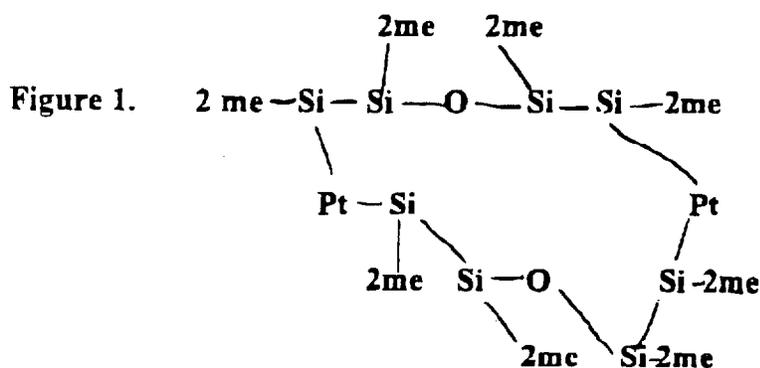
Department of Pathology
TEL: (713) 798-4661
FAX: (713) 798-5838

Platinum Toxicity Response by Ernest D. Lykissa Ph.D. to Doug Peters Esq. 3/18/99

Dear Sir,

Complexed Platinum especially in the bound form with silane moities in the +4 oxidation state do exist as the evidence of lipid solubility of these complexes has shown

(Lykissa, 1997). It appears that the defendants position that the platinum found in the gel of breast implants is of zero valence is based on the erroneous assumption that since the platinum is bound to silane chemical groups, it has no charge available for further chemical bonding. Once the silane moieties are sheered off the platinum molecule, the +4 charges of the platinum molecule become available. At this ionic state the platinum molecule may bond with sulfhydryl groups of the cysteine amino acid residues of proteins and thus disrupt their structure and inhibit their functions as enzymes. These may be vital for maintaining key physiological or biological functions. This is supported by the data presented by Agnew et al, in which platinum inhibits the action of numerous enzymes. Platinum silane complexes are highly lipophilic due to the absolute absence of any hydroxyl molecular bonding which would inhibit the catalytic action that one wants to render so that the cyclo-polydimethylsiloxane mixture may begin its crosslinking with neighboring silicon molecule to neighboring silicon molecule by trapping oxygen from the water vapor which is fed into the reaction mixture for this sole purpose. We duplicated this hydrosilation process at 140 degrees Celcius during the production of the distillate and thus we proved the reversibility of the catalytic action of the platinum silane catalyst. The platinum-silane catalyst molecule as it is shown in figure 1 demonstrates the template that the platinum silane provides, for the seeding of the crossed-linked cyclosiloxane organic-crystal formation (sic. gel that breast prosthetic devices were filled with). This catalytic action during optimum reaction conditions is absolutely reversible due to the vapor pressure differential created by aspiration of moist air over the molten crosslinked gel (Lykissa et al, 1997). The proof of the valence +4 ionic state of the platinum is that the platinum silane complex is distillable at 140 degrees Celcius. Nobody may claim with scientific merit that platinum metal may be vaporized at 140 degrees Celcius. We have obtained numerous distillates of this gel that always contained platinum-silane as our Inductively Coupled Argon Plasma-Mass Spectrometric measurements showed in the same scientific communication by our team.



The publications by Lykissa and his colleagues in 1998 and 1999, attempted to concentrate on the possible toxic effects of siloxanes. One is the most recent publication in the DHHS sponsored Environmental Health Perspectives (Lieberman et al, 1999). In this communications the data clearly shows that cyclosiloxane- platinum silane (distilate) is toxically equivalent to toxins like carbon tetrachloride (equivalent median lethal dose LD50).

In addition these cyclosiloxanes that so easily bleed through the breast implant envelopes are capable of resulting into lung congestion among others by coalescing apparently on the alveolar membranes where the oxygen-carbon dioxide exchange occurs during respiration. In the hot breathing living lung the cyclosiloxanes encounter hot water vapor that makes them obstruct the membrane surfaces needed for the vital gas exchange described above. If the dose is high enough when administered by the intraperitoneal route, it may result in massive blockage of the pulmonary alveolar space, and death may ensue. It was clearly demonstrated that the low molecular silicone bleed which is complexed with expended platinum silane catalyst not only accumulate in tissues including brain, ovaries, kidneys, liver and lungs, but this silicone-platinum-silane effluent from the breast implants, is also capable of fatal lung and liver syndromes in high enough concentrations. (Kala et al 1998, Lieberman et al 1999).

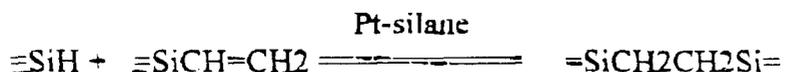
The author(s) of the defendants response assume a position of authority by labeling Dr. Harbut's medical opinion as erroneous though not been medical doctors or even medical practitioners but rather retired spectroscopist chemists, (i.e. Dr. Ziegler) or some other synthetic chemist combination. It is obvious that even their theoretical assertions have no base since they do not take in consideration the reversibility of the process they assumed so stable and inert till, it was proven by our team otherwise.

The evidence presented in the American Journal of Pathology in March 1998 by Lykissa and his colleagues, clearly demonstrates the propensity of the cyclosiloxane-platinum silane mixture, to accumulate in the brain tissue of living animals and to persist there for the duration of one year following a single administration.

It is highly unlikely, that the rich in lipids brain tissues, that depend to a great extent on lipophilicity (lipid solubility) for the transmission of electric, in nature, nerve impulses are not affected by high concentrations of very lipid soluble cyclosiloxane-platinum silane toxins, residing on the membranes of their constituent cells. The scientific work of Agnew et al provides a very powerful piece of evidence that platinum ions in the brain area either as electrodes carrying an electric charge or platinum metal in the presence of intense electric discharges resulted by a living brain.

We have proven that the catalyst is active because the reaction is reversible when the conditions of production where emulated with moist air aspirated (drawn out) instead of pumped into the reaction mixture.

The defendants figure 1: Hydrosilation Reaction has one major "overlook"



The arrows unlike their depiction of a single reaction arrow, like in every chemical catalytic reaction point in both directions of synthesis and dissociation governed by a constant (K equilibrium) of the reaction.

This equilibrium constant is active both during the formation of the silicone crosslinking for the creation of the silicone gel, and the dissociation of the gel during reversal to its toxic components cyclosiloxanes and expended platinum-silane catalyst.

Earlier discussed evidence (Lykissa et al 1997, Kala et al 1998) clearly demonstrate this to be untrue. Platinum silane does dissolve in fats and is distributed into the body i.e. brain tissue where it persists for long periods of time.

The defendants describe a process like I have been discussing earlier where the hydrosilation curing of the gel occurs in the presence of a very active Platinum +4 molecule which needs to be harnessed in the presence of excess silane 1:10,000 fold excess. If the platinum molecule in this reaction is so inert as they seem to claim, to be in the metal state, then what was the purpose of such excess silane, if not for harnessing the high reactivity of platinum.

The various modifications show different methods of stabilizing and neutralizing various byproducts of the catalyst manufacture. The clue is in the solvent solubilizing agent found in Table 1 of the defendants response.

Butyl Carbitol Acetate produces the evolution of acetic acid when this catalyst comes in contact with the other reactive molecules, a very toxic irritant, similar to very concentrated distilled vinegar. It also acts as a solvent carrier for a lipophilic molecular complex. Ethanol was addressing the lipid solubility of the substance while the neutralization with sodium-bicarbonate washes was for the purposes of ridding the mixture of chlorine ions capable of forming hydrochloric (muriatic) acid in the tissues. Obviously the manufacturers of MDF-0069 and XY-173 never addressed the issue of hydrochloric acid or acetic acid and further additional complex toxic release issues. Especially when the breast implants containing this type of gel expended platinum catalyst were implanted in a human female chest area and begun to leak their contents in the surrounding tissues.

In the presentation of the Lewis data, one finds reference to the Lewis finding, that Platinum silane catalyzed reactions produce yellow color, and that yellow hue disappears when large concentrations of platinum colloidal aggregates are not allowed to form therefore again we find contradictions as to the presence of colloidal platinum silane. Here the authors of the defendants offer a hypothetical assertion at best, that maybe the aggregates are so fine that no color is seen in the gel.

We stated in our publication that the gel implants were intact and we ensured ourselves of this fact by washing the outside with water and then performing a number of wipe test with soft cotton and never showing any detectable cyclosiloxanes or platinum by gas chromatography/ mass spectrometry. This was part of good laboratory practice.

The defendants discuss the failure of Dr. Ash to find platinum in the urine of women with silicone breast implants. Based on the evidence we have presented the lipid solubility of these platinum-cyclosiloxane complexes are to be excreted in the sebum (people's oil) and the feces, and not in the urine. We have ongoing studies to demonstrate the validity of this.

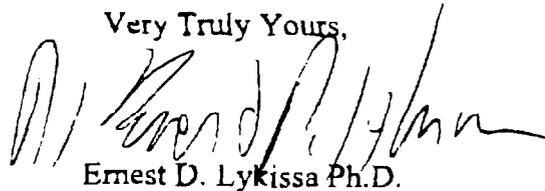
The data published by our team in 1998 as we mentioned earlier clearly shows that these complexes accumulate in the kidney and brain. These complexes have been

shown by Agnew et al to result in toxic interactions (inhibitions) of the brain enzymes. But yet the authors of the defendants choose to ignore the preponderance of the scientific evidence.

The defendants in their conclusion seem to claim erroneous facts about the reactivity (valence state) of the platinum catalyst and the lack of allergic properties by this substance when very early it was shown that platinum metal powder in platinum miners is highly allergenic and results in an asthma-like syndrome.

In conclusion, I find the defendants supplemental submission misleading and in significant part, wrong on the known science

Very Truly Yours,



Ernest D. Lykissa Ph.D.

C. DR. HARBUT'S REPLY

CENTER FOR OCCUPATIONAL & ENVIRONMENTAL MEDICINE, P.C.

March 15, 1999

22255 GREENFIELD ROAD, SUITE 440
SOUTHFIELD, MICHIGAN 48075

248) 559-6663
FAX 248) 559-8254

J. Douglas Peters, Esq.
Charfoos & Christensen, P.C.
5510 Woodward Avenue
Detroit, Michigan 48202
Fax: 313-875-8522

Dear Mr. Peters,

Thank you for allowing me to respond to the "Defendant's Supplemental Submissions of the Chemistry and Toxicology of Platinum."

The available science is in dispute with many of the defendants' statements.

I understand that other workers will be contributing detailed information in regard to the specific chemical and valence form of the platinum catalyst involved, but it has been my belief that platinum catalysts are contained in, and released from both the silicone shell and gel. This belief is founded in part in the work of Dr. Omar Henderson of the Centers for Disease Control; Drs. El-Jammal and Templeton of the University of Toronto; Baylor University's Dr. Ernest D.

Lykissa); the work of Dr. David Zimmerman; the expressed beliefs of David H. Sanders, President, SURGITEK; and the presence of local and systemic disease consistent with causation by platinum salts in women with silicone gel breast implants, which will be discussed later in this letter.

Because of the enormous potency of platinum salts, NIOSH has set an airborne platinum salt 8-hour threshold limit value at .003mg-m³ for non-sensitized exposed persons. There are no available data for "safe" levels of platinum salt-containing implanted devices. Drs. Niezborala and Garnier state, however, in regard to industrial contact, "At no stage should a worker be able to come into contact with a solution or a solid containing these particular complex platinum salts."⁷

There is greater than or equal to 2 mg of platinum catalyst residual in two 250 mg silicone gel breast implants.

Platinum salts are considered so toxic that the consensus opinion in Occupational Medicine is that platinum allergy exists in a worker presenting with classic allergy symptoms (who is exposed to platinum salts) until proven otherwise.⁸

Much of what we know about these classic symptoms have been as a result of external platinum salt exposure and have been tabularized to include (1) Rhinorrhea (2) Sneezing (3) Itching of nose, throat, palate (4) nasal congestion (5) Cough (6) Dyspnea (7) Asthmatic Wheezing (8) Cyanosis (9) Conjunctivitis (10) Edema of eyes (11) Lacrimation (12) Redness of eyes (13) Itching of Eyes (14) Photophobia (15) Urticaria (16) Angioedema (17) Contact Dermatitis (18) Pruritia (19) Lymphocytosis (20) Eosinophilia.⁹

"Workers exposed to platinum salts who present with the signs and symptoms discussed above should be considered to have platinum allergy until proven otherwise, and a trial of removal from exposure may be warranted."¹⁰

The literature contains other reports of health effects of platinum salts.

Agnew, et al injected 10 to 30 micrograms of a 10 ppm solution of 75% PtCl₄ and 25% PtCl₆ into the brains of cats.¹¹ They induced membranous cytoplasmic bodies, zebra bodies and multiple nucleoli. They noted that the induction of zebra bodies and MCBs, both of which are morphologic features of human neuropiloidoses associated with congenital enzyme deficiencies. This pathology suggests an inhibitory effect of platinum on brain enzymes. In other words, platinum salts cause brain disease. It is important to note the concentrations of toxin used here.

Nordlind reported Platinum Chloride (PtCl₂) to inhibit cell DNA synthesis at 10⁻⁴ to 10⁻⁵ Molar concentration, but to stimulate mainly thymocytes at 10⁻⁵ to 10⁻⁶ Molar concentrations.¹²

Dr. Schuppe investigated the requirements for sensitization to complex salts of platinum in a mouse model by means of the popliteal lymph node assay. A single subcutaneous injection of dissolved hexachloroplatinates without adjuvant induced a vigorous primary immune reaction in the draining PLN. Peak reactions were obtained around day 6 post-injection of 90-180 nmole of $\text{Na}_2(\text{PtCl}_6)$. Primed mice mounted an enhanced response upon local re-stimulation with sub-optimal doses of the same, but not unrelated compounds, indicating a specific secondary response. For elicitation of a secondary response to $\text{Na}_2(\text{PtCl}_6)$, one fifth of the primary dose proved to be sufficient. Compared with most other drugs and chemicals tested, the amount of halide Pt salts inducing maximal PLN reactivity was very low.

Compounds eliciting PLN reactions include contact sensitizers and drugs that can induce various types of allergy and auto-immunity or both. Schuppe found a genetic component to the PLN response to hexachloroplatinate. T cells were required to elicit PLN reactions to the $(\text{PtCl}_6)^{2-}$.¹³

Dr. Bloksma and colleagues reviewed results obtained with popliteal lymph node assays in rodents and discussed their ability to detect and analyze immunotoxic effects of drugs and other low molecular weight chemicals. They reported Dr. Schuppe's work in support of their thesis, i.e.: hexachloroplatinate evokes a primary and secondary immune response, with T-Cell dependence and B-Cell activation. It is included as part of an approach to recognize sensitizing or otherwise immunomodulating chemicals.¹⁴

This work was preceded by Pepys work as far back as 1978 when he confirmed the presence of specific IgE antibody to platinum salts, but also heat stable, short-term sensitizing antibodies, presumably STS-IgG.¹⁵ By 1988, Seiler had reported that while IgE antibodies mediate the immediate reaction at re-exposure, IgG antibodies are responsible for the delayed effects.¹⁶

As work in the field of platinum salt sensitivity becomes more sophisticated, the role of IgE levels have become less predictive of the pathophysiology induced by platinum salts than previously believed. Merget and colleagues described the course of immediate-type occupational asthma after allergen avoidance. After removal from direct exposure, IgE dropped, but the authors concluded that both nonspecific and specific bronchial responsiveness do not decrease after removal from exposure in immediate-type asthma caused by platinum salts.¹⁷

In fact the variability of RAST testing, skin prick testing and Serum IgE are so variable and often insensitive, we are cautioned that negative tests even in the occupational setting do not exclude platinum allergy.¹⁸ Merget reported 9 platinum-salt exposed workers previously without work-related symptoms who converted from a negative to a positive skin prick test. Two of the group had a marked increase in total IgE, but for the whole group, total IgE did not show an increase at after skin test conversion.¹⁷

There were some specific areas in which the authors of the defense position on this issue weren't as clear as they might have been:

"Platinum metal is non-toxic and non-allergenic". Although this is felt to be largely true, there are reports in the literature of toxicity and allergenicity of platinum metal. There are reports of contact stomatitis due to palladium and platinum in dental alloys, contact dermatitis due to metallic platinum, the postulate that soluble nonchlorinated platinum compounds may be allergenic, and that a fine powdered form of platinum metal may also be allergenic."^{21, 22, 23}

"Platinum exposure is common in the General Population". In this section, the authors state, "Dr. Ash and his colleagues concluded that 'urine platinum is highly unlikely to be increased as a result of breast implants."

I have provided the rest of the article with this letter. The cited paragraph is fundamentally an explanation of an earlier paragraph which states, "Indeed, urine would appear to be a poor specimen for the evaluation of chronic platinum exposure, given that half of the platinum in blood is eliminated in <3 days and that the affinity of platinum for adipose tissue is high."²⁴

Incidentally, it was our facility which first noticed the incorrect urinary platinum levels being reported nationally and we sent triple samples to different labs to attempt to learn the reasons for what we thought were false elevations. The confirming correspondence is attached as Appendix A, although this material was already subpoenaed and provided, as was our notification of the FDA. Dr. Nuttall later apologized to me for excluding an acknowledgement.

"Only some platinum salts induce allergic responses" and "Platinum Salt Allergy". Much of this section has been rebutted above. Please note the protean manifestations of "platinum salt allergy." Also please note the platinum salts which have been associated with allergic responses are also associated with silicone breast implants.

"There is no evidence of platinum-salt allergy in women with silicone breast implants." This section seemed like an excuse to attack my recent work published in the Israel Journal of Occupational Health. The authors' footnote #86 is not very accurate.

The articles referenced in notes 7, 8, 10, 13, 14, 15, 17 and 22 explain how platinum salts can cause systemic hypersensitivity as a function of immunologic initiation rather than irritant epithelial effect. Furthermore, all of the publication's cases of asthma were diagnosed using criteria consistent with both the ATS and NIH guidelines.

Attached as Appendix B are the results of my Pulmonary Function Testing of this patient population. Appendix C is a letter from the National Institute for Occupational Safety and Health approving the Center for Occupational and

Pepys J, Parish WE, Cromwell O, Hughes KE. Passive transfer in man and the monkey of Type I allergy due to heat labile and heat stable antibody to complex salts of platinum. *Clinical Allergy*, 1979, Vol 9: 99-108

Seiler HG, Siege H. *Handbook on toxicity of inorganic compounds*. New York: Marcel Dekker, 1988: 341-344, 501-574

Rohg M, Reineke M, Rueckmann A, Beremund E-M, Schmitz-Werninghaus G. Nonspecific and specific bronchial responsiveness in occupational asthma caused by platinum salts after allergen avoidance. *Am J Respir Crit Care Med* 1994; 150: 1146-9

¹⁷ see 14

Merget R, Caspari C, Kuller R. The Sequence of Symptoms, Sensitization and Bronchial Hyperresponsiveness in Early Occupational Asthma due to platinum salts. *Int Arch Allergy Immunol* 1995; 107: 406-407

Koch P, Baum H-P. Contact stomatitis due to palladium and platinum in dental alloys. *Contact Dermatitis*, 1996; 34: 253-257

²¹ Sheard C. Contact Dermatitis from Platinum and Related Metals. *AMA Archives of Dermatology*, 1955

²² Casarett and Doull's *Toxicology*. Third edition. Macmillan Publishing Company, 800 Third Avenue, New York, New York 10158: 622

²³ see 14, p 876

²⁴ Nuttall K, Gordon WH, Ash KO. Breast implants and urinary platinum. *Clinical Chemistry*, Vol 40, No 9, 1994: 1787

²⁵ Tueber S, Howell L, Yoshida S, Gershwin. Remission of Sarcoidosis following removal of silicone gel breast implants. *Int Arch Allergy Immunol*, 1994; 105: 404-407

²⁶ Quinn K. Silicone gel in scar treatment. *Burns*, 1987; 13: 333-340

V. SUMMARY AND CONCLUSION

The Parties agree that "platinum salts" (aka chloroplatinic acid) can cause systemic disease in humans as a result of toxic and/or hypersensitivity reactions. These toxic and hypersensitivity reactions can range from asthma, rhinorrhea, tinnitus, conjunctivitis, urticaria, fatigue syndromes secondary to impaired oxygen exchange, neurotoxicity, sicca syndrome, and macular rashes.

The Plaintiffs' Submission proves that silicone gels and elastomers do contain unreduced chloroplatinic acid, i.e., "platinum salts." The Defendants' internal documents, the testimony of Defendants' employees, and the admissions

of the Defendants in their Supplemental Submission on Platinum constitute such compelling proofs that a fairminded scientific review can reach only one conclusion.

Plaintiffs Submission on Platinum also shows that, (even if one buys the “scientific position” of Defendants, i.e., that all platinum salts are reduced to sub-micron sized elemental particles in colloidal suspension), in susceptible individuals, sub-micron sized elemental platinum, platinum in colloidal suspension, and platinum metal, can each be a toxin and/or a hypersensitizer in humans.

Plaintiffs further establish, through the submission of Dr. Wabeke, that the amount of platinum in silicone gel elastomers and implants is not a “small amount” but rather, a tremendous amount, i.e., as much as “1000 x the permissible occupational exposure.”

Finally, based on the extensive peer reviewed research published on elastomer shunts we find a decades long track record of hypersensitivity disease, hypersensitivity complications and elastomer shunt failures. Because silicone elastomers (e.g., shunts) have ten times as much platinum catalyst as silicone gels, the extensive rate of shunt toxicity and hypersensitivity complications cannot surprise the Defendants. Why would we expect a different result from the gels and elastomers in breast implants?

In conclusion, specifically as to individual patients with individual signs and symptoms, and generally, as to the mechanisms of toxicity and hypersensitivity as outlined in this Submission, a compelling medical and scientific case is made that platinum salts, as a residual contaminant in silicone gels and elastomers are a probable factor, or co-factor, in a variety of the complaints and diseases presented

by women exposed to silicone gels and elastomers. These facts compel a conclusion that, silicone gels and elastomers can cause systemic disease in humans.

A. Templeton Reply Footnotes:

57. Templeton (See Plaintiffs' Supplemental Submission, Exhibit 11, Record No. 7390).

B. Lykissa Reply Footnotes:

58. Lieberman, M. W., Lykissa, E.D., Barrios, R., Ou, Ching Nan, Kala, G., Kala, S.V. "Cyclosiloxanes Produce Fatal Liver and Lung Damage in Mice." Environmental Health Perspectives, Vol. 107, No. 2 (February 1999). [See Plaintiffs' Supplemental Submission, Exhibit 18, Record No. 7406]

59. [See Plaintiffs' Supplemental Submission, Exhibit 51, Record No. 7439]

60. [See Plaintiffs' Supplemental Submission, Exhibit 50, Record No. 7438]

- 58.** Michael W.Lieberman, Ernest D. Lykissa, Roberto Barrios, Ching Nan Ou, Geeta Kala and Subbarao V. Kala. Cyclosiloxanes Produce Fatal Liver and Lung Damage in Mice. *Environmental Health Perspectives* Volume 107, Number 2, February 1999.

Kala SV, Lykissa ED, Neely MW, Lieberman MW. Low molecular weight silicones are widely distributed after a single subcutaneous injection in mice. *Am. J. Pathol.* 152:645-649 (1998).

- 59.** Black RC, Hannaker P. Dissolution of smooth platinum electrodes in biological fluids. *Appl. Neurophysiol.* 42:366-374 (1979).

- 60.** Agnew WF, Yuen TGH, Dudenz RH, Bullara LA. Neuropathological effects of intracerebral platinum salt injections. *Surg. Neurol.* 4:438-448, 1975.

C. Harbut Reply Footnotes:

- 1&2. [Exhibit 61, Record No. 7446]
3. [Exhibit 62, Record No. 7447]
4. [Exhibit 63, Record No. 7448]

5. [Exhibit 64, Record No. 7449]
6. [Exhibit 65, Record No. 7450]
7. [Exhibit 66, Record No. 7451]
8. [Exhibit 67, Record No. 7452]
9. [Exhibit 68, Record No. 7453]
10. [Exhibit 69, Record No. 7454]
11. [Exhibit 70, Record No. 7455]
12. [Exhibit 71, Record No. 7456]
13. [Exhibit 72, Record No. 7457]
14. [Exhibit 73, Record No. 7458]
15. [Exhibit 74, Record No. 7459]
16. [Exhibit 75, Record No. 7460]
17. [Exhibit 76, Record No. 7461]
18. [Exhibit 77, Record No. 7462]
19. [Exhibit 78, Record No. 7463]
20. [Exhibit 79, Record No. 7463]
21. [Exhibit 80, Record No. 7464]
22. [Exhibit 81, Record No. 7465]
23. [Exhibit 82, Record No. 7466]
24. [Exhibit 83, Record No. 7467]
25. [Exhibit 84, Record No. 7468]
26. [Exhibit 85, Record No. 7469]

HARBUT EXHIBIT NOS. & FOOTNOTES:

Exs. Fns.

61. ^{1,2} 1) Personal Communication "Platinum Toxicity and Breast Implants Conference Call": May 9, 1996, 3:00 p.m., EST. Roster has been subpoenaed and provided; 2) E-Mail from Raymond E. Biagini, Ph.D., DABT, NIOSH; 4.23.96. Document has been subpoenaed and provided.
62. ³ El-Jammal A, Templeton DM: Measurement of platinum in biomedical silicones by ICP-MS. *Anal.Proc.*: VOL 32, Iss 8, 1995; 293-5
63. ⁴ Baylor University's Dr. Ernest D. Lykissa
64. ⁵ Philen R, Henderson, LO, et al: Does Platinum in Silicone Breast Implants Cause Immune-Mediated Hypersensitivity?, non-funded CDC research proposal. Dr. Zamierowski found platinum at over 100ppb in the outer lumens of double lumen implant. Document has been subpoenaed and provided.
65. ⁶ MED00022435-22448
66. ⁷ Niezborala M, Garnier R. Allergy to complex platinum salts: a historical prospective cohort study. *Occup Environ Med* 1996; 53: 252-257.
67. ⁸ Hazardous Materials Toxicology: clinical principles of environmental health. Sullivan JB II, Krieger, Gary R. 1192. Williams & Wilkins, 428 East Preston Street, Baltimore, Maryland 21202. 879.
68. ⁹ *ibid.* p877. Table 82.2, adapted from BoggsPB. Platinum allergy. *Cutis*. 1985; 35:318-320
69. ¹⁰ Occupational and Environmental Respiratory Disease. Harber P, Schenker M, Balmes J; Mosby Year Book. 11830 Westline industrial Drive, Stl Louis, Missouri 63146. 1996. 501.
70. ¹¹ Agnew WF, Yuen TGH, Pndenz RH, Bullara LA Contract NO NO1-NS-O-2275, National Institute of Neurological and Communicative Diseases and Stroke, Bethesda, Md. Huntington Institute of Applied Medical Research, Pasadena, California.
71. ¹² Nordlind K. Further Studies on the Ability of Different Metal Salts to Influence the DNA synthesis or Human Lymphoid Cells. *Int. Arcs Allergy apl. Immun.* 79: 83-85 (1986)
72. ¹³ Schuppe. HC, Haas-Raida D, Kulig J, Boemer U, Gleichmann E, Kind P. T-Cell-dependent popliteal lymph node reactions to platinum compounds in mice. *Int. Arch. Allergy Immunol.* (1992) 97(4), 308-14.
73. ¹⁴ Bloksma N, Kubicka-Muranyi M, Schuppe H-C, Gleichmann E, Gleichmann H. Predictive Immunotoxicological Test Systems: Suitability of the Popliteal Lymph Node Assay in Mice and Rats. *Critical Reviews in Toxicology*. 25(5):369-396 (1995).
74. ¹⁵ Pepys J, Parish WE, Cromwell O, Hughes KEG. Passive transfer in man and the monkey of Type I allergy due to heat labile and heat stable antibody to complex salts of platinum. *Clinical allergy*, 1979, Vol 9. 99-108
75. ¹⁶ Seiler HG, Siege H. Handbook on toxicity of inorganic compounds. New York: Marcel Dekker. 1988. 341-344. 501-574.
76. ¹⁷ Rolg, M, Reineke M, Rueckmann A, Bergmann E-M, Schultze-Werninghaus G. Nonspecific and specific bronchial responsiveness in occupational asthma caused by platinum salts after allergen avoidance. *Am J Respir Crit Care Med* 1994; 150: 1146-9.
77. ¹⁸ see 14.
78. ¹⁹ MergetR, CaspariC, Kulzer R. The Sequence of Symptoms, Sensitization and Bronchial Hyperresponsiveness in Early Occupational Asthma due to platinum salts. *Int Arch Allergy Immunol* 1995; 107:406-407
79. ²⁰ Koch P, Baum H-P. Contact stomatitis due to palladium and platinum in dental alloys. *Contact Dermatitis*, 1996, 34. 253-257.
80. ²¹ Sheard C. Contact Dermatitis from Platinum and Related Metals. *AMA Archives of Dermatology*. 1955
81. ²² Casarett and Doull's Toxicology. Third edition. Macmillan Publishing Company 866 Thrid Avenue, New York, New York. 1986. 622.
82. ²³ see 14. p 876. Id.
83. ²⁴ Nuttall K, Gordon WH, Ash KO. Breast implants and urinary platinum. *Clinical chemistry*. Vol 40, No.9, 1994. 1787
84. ²⁵ Tueber S, Howell L, Yoshida S, Gershwin. Remission of Sarcoidosis following removal of silicone get breast implants. *Int Arch Allergy Immunol*. 1994; 105:404-407.
85. ²⁶ Quinn K. Silicone gel in scar treatment. *Burns*. 1987. 13. s33-s40

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ALABAMA
SOUTHERN DIVISION

IN RE: SILICONE GEL BREAST :
IMPLANT PRODUCTS LIABILITY :
LITIGATION (MDL-926)

MASTER FILE NO.
CV 92-P-10000-S

PROOF OF SERVICE

STATE OF MICHIGAN)
) SS:
COUNTY OF WAYNE)

J. Douglas Peters, being first duly sworn, deposes and says, that on the 25th day of March, 1999, he served copies of Plaintiffs' Supplemental Submission on the Chemistry and Toxicology of Platinum and Record References and Proof of Service via UPS Next Day Air upon:

Nathan Schachtman
McCarter & English
1820 Chapel Avenue, West
Suite 380
Cherry Hill, NJ 08002

George Link
Brobeck, Phleger & Harrison
550 South Hope Street
Suite 2300
Los Angeles, CA 90071

Jane Fugate Thorpe
Alston & Bird
One Atlantic Center
1201 W. Peachtree Street
41st Floor
Atlanta, GA 30309

John Donley
Kirkland & Ellis
200 E. Randolph Drive
Chicago, IL 60607

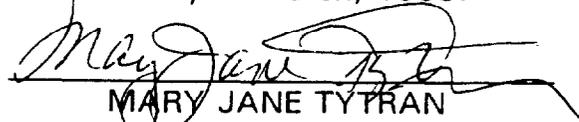
Ina Leonard
University of Alabama, Birmingham
820 AB
Birmingham, AL 35294

John Kobayashi
The Kobayashi Law Firm
1633 Fillmore Street
Suite 210
Denver, CO 80206

The Hon. Sam C. Pointer, Jr.
United States District Court
1729 5th Avenue, N.
822 Federal Courthouse
Birmingham, AL 35203


J. DOUGLAS PETERS

Subscribed and sworn to before me
this 25th day of March, 1999.


MARY JANE TYTRAN
Notary Public, Oakland County, MI
Acting in Wayne County
My Commission Expires: 08/21/01

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22255 Greenfield Rd. Suite 440
Southfield, MI 48075

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First Class Mail

Food and Drug Administration
ockets Management Branch (HFA)
Room 1-46 Park Bldg.
12420 Parklawn Drive
Rockville, MD 20857