UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ALABAMA
Southern Division

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

SUBMISSION OF RULE 706 NATIONAL SCIENCE PANEL REPORT

MAY IT PLEASE THE COURT and the Parties (and all interested members of the public):

The Rule 706 National Science Panel appointed by this Court respectfully submits its report pursuant to this Court's Order No. 31C (Appointing Members of National Science Panel).

Copies are being hand-delivered from my office to designated lawyers for Plaintiffs and Defendants.

Respectfully submitted as of the 30th day of November, 1998.

THE KOBAYASHI LAW FIRM, P.C.

By: John M. Kobayashi /by LMB

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November 19, 1998

The Honorable Sam C. Pointer, Jr.
Chief Judge, United States District Court
Northern District of Alabama
US Courthouse, Room 882
1729 5th Avenue North
Birmingham, AL 35203

Dear Judge Pointer:

The National Science Panel appointed by you to evaluate the scientific data on Silicone Breast Implants In Relation To Connective Tissue Diseases and Immunologic Dysfunction has completed its report. We are eager for the report to be received by you and the relevant parties since this has been a prolonged and time-consuming process. To expedite this goal, we have sent five hard copies of the final report to Mr. John Kobayashi on Wednesday November 18, 1998 by express mail for next day delivery.

Concurrently, this letter of transmittal to you is being circulated by express mail to each panel member for signature. This signed letter should arrive at Mr. Kobayashi's office by Wednesday November 25 and should accompany the copy (s) of the report that Mr. Kobayashi sends to you shortly thereafter.

The executive summary and each chapter in the report has been reviewed multiple times by each Panel member, and we are in general agreement on the contents of the report. However, the Panel as a group has relied heavily on the specialized expertise of each Panel member for the specific information provided in the individual chapters.

We are pleased to have completed this phase of the project and are hopeful that subsequent activities required of the panel may be conducted expeditiously. We are particularly appreciative of your efforts to ensure a responsible process, both legally and scientifically, to the conduct of our work.

Sincerely,

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Silicone Breast Implants in Relation to Connective Tissue Diseases and Immunologic Dysfunction

A Report by a National Science Panel to the Honorable Sam C. Pointer Jr., Coordinating Judge for the Federal Breast Implant Multi-District Litigation

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Barbara S. Hulka

Nancy I. Kerkvliet

Peter Tugwell

17 November 1998

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Silicone Breast Implants in Relation to Connective Tissue Diseases and Immunologic Dysfunction

Executive Summary

Four scientific experts in the fields of immunology, epidemiology, toxicology, and rheumatology were appointed by the Honorable Sam C. Pointer, Jr., Coordinating Judge for the Federal Breast Implant Multi-District Litigation, to serve on a National Science Panel. Members of the panel include:

Betty A. Diamond, MD, Professor, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York;

Barbara S. Hulka, MS, MD, MPH, Kenan Professor, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina;

Nancy I. Kerkvliet, MS, PhD, Professor of Toxicology and Extension Toxicology Specialist, Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, Oregon; and

Peter Tugwell, MBBS, MD, MSc, FRCP [Canada and United Kingdom], Professor and Chairman, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada.

The panel was instructed to review and critique the scientific literature pertaining to the possibility of a causal association between silicone breast implants and connective tissue diseases, related signs and symptoms, and immune system dysfunction. The panel met, received instructions from the judge, and heard testimony from experts selected by the counsels for the plaintiffs and for the defendants in October 1996. Additional hearings were held in July 1997, when experts identified by the parties provided testimony, and in November 1997 when the panel's invited experts presented their research material.

In spring 1997, over 2000 documents were submitted to the panelists from the legal counsels for both parties. Subsequently, the counsels pared these numbers down to the approximately 40 most important documents from each side for each panel member. The source of references, whether counsel for the plaintiffs or counsel for the defendants, was not identified to the panelists. The panel members also used their own literature search strategies, and were neither limited to nor obligated to use those submitted by the respective legal counsels.

Organization of Report

The report is divided into four chapters, each based on the expertise of one of the four panelists. They follow in sequence: toxicology, immunology, epidemiology, and rheumatology. A summary and bibliography are provided at the end of each chapter and some chapters contain appendices. This executive summary precedes the chapters to state the judge's charge to the panelists, indicate the process undertaken by the panel, and provide a brief overview of the panel's main findings and conclusions.

Charge from Judge Pointer

The court-appointed experts were asked to respond to the following questions:

> "(a). Issues. To what extent, if any and with what limitations and caveats do existing studies, research, and reported observations provide a reliable and reasonable scientific basis for one to conclude that silicone-gel breast implants cause or exacerbate any of the conditions described in (b) below? If, in the process of making these findings, you believe that there are related or subordinate issues that should be separately addressed, please do so.
>
> (b). Scope. You are asked at this time to consider the relationship, if any, between implants and the following:
>
> 'classic' connective tissue diseases, such as systemic lupus erythematosus, Sjögren's syndrome, etc.
>
> 'atypical' presentations of connective tissue diseases or symptoms immune system dysfunctions

Listed in the appendix to this order are various diseases, symptoms, conditions, or complaints that have sometimes been asserted as possibly associated with silicone-gel implants. To the extent you believe appropriate and without being asked to address separately each of these diseases, symptoms, conditions, and complaints you are encouraged to comment on the scientific basis, if any, for any such claimed linkage. You are not being asked to consider purely local complications, such as breast disfigurement, tenderness, or capsular contracture.

(c). Contrary Opinions. To what extent, if any, should any of your opinions referenced in (a) above be considered as subject to sufficient genuine dispute as would permit other persons, generally qualified in your field of expertise, to express opinions that, though contrary to yours, would likely be viewed by others in the field as representing legitimate and responsible disagreement within your profession?"

Background to Charge

While silicone breast implants have been in use since the early 1960s, it was not until 1976 that legislation was passed giving the Food and Drug Administration (FDA) responsibility to oversee the safety of medical devices. Because implants had been used for over a decade, their safety was presumed and their continued use was permitted. Furthermore, while it was known that local complications could occur with silicone breast implants and that rupture of the implant occurred in a portion of recipients, safety studies in animals had suggested no systemic toxicity of silicone gel. In 1982, the FDA proposed that the manufacturers of implants should provide additional evidence on the safety of breast implants. In 1988, the FDA mandated that manufacturers provide such evidence. This ruling was not enforced until 1991, when public attention became focused on the question of the risks of implants and their possible association with connective tissue diseases. The FDA convened two advisory committees in 1991. After the first, David Kessler, then head of the FDA, asked for a voluntary moratorium on the use of silicone gel-filled implants; after the second in 1992, he banned their use except in clinical trials of breast reconstruction after cancer surgery. He stated that the ban was implemented not because gel-filled implants had been shown to be unsafe, but rather, that the manufacturers had not provided adequate data proving their safety.

The first suggestion that there might be adverse systemic reactions to augmentation mammoplasty were reports of autoimmune disease in Japanese women who received liquid paraffin or silicone injections for breast augmentation. Subsequently, concerns were raised regarding an association of silicone breast implants with classic connective tissue diseases and less well-defined atypical syndromes. These initial concerns were expressed in case reports in the medical literature and raised the call for examination of the effects of silicone on the immune system. In December 1990, Connie Chung reported in a nationally televised program that breast implants might be unsafe. Although litigation against the manufacturers of breast implants started in 1982, the number of suits brought by women claiming that they had developed systemic connective tissue disease following silicone breast implantation increased markedly in the 1990s. It has been in this adversarial atmosphere, with high stakes for plaintiffs and defendants, that immunologic and epidemiologic studies of silicone and silicone breast implants have been performed.

Major Findings and Conclusions

Toxicology

Testing of chemicals, pharmaceuticals, and other products in animal models serves to prevent potentially hazardous compounds from reaching the human population. Animal toxicology studies provide information regarding the potential toxicity of a substance, the doses required to elicit toxicity, and the spectrum of possible toxic effects. Because potentially confounding variables (e.g., age, sex, environmental factors) can be controlled experimentally, animal studies provide information that often cannot be obtained directly in humans.

Toxicologic testing with silicone goes back almost 50 years. In the early years, silicone had an enviable record of safety, having been shown consistently to be inert with respect to systemic effects. Only, localized reactions analogous to those induced by other foreign bodies were observed. However, in the late 1980s, case reports of a possible link between silicone breast implants and autoimmune diseases in women reinvigorated toxicologic testing of silicone gels and related compounds. The majority of these more recent studies reaffirmed the low systemic toxicity of silicone.

Animal studies have addressed the possibility that silicone may promote systemic disease in women by acting as an adjuvant or an antigen to induce immune responses, by altering normal

regulation of the immune system, or by inducing systemic inflammation. These potential effects have been tested in specialized animal models of autoimmune diseases. The preponderance of data from these studies indicate that silicone implants do not alter incidence or severity of autoimmune disease. Although silicone gel has been shown to possess weak adjuvant activity when it is injected as an emulsified preparation with a foreign antigen, there is no evidence that silicone breast implants precipitate novel immune responses or induce systemic inflammation. The only reasonably consistent effect of silicone on the immune system in animals is a depression in natural killer cell activity. However, no physiologic consequence of this depression has been demonstrated.

Considering the broad range of testing systems that have been used in the study of silicone effects, the toxicologic and immunologic responses are few in number and questionable in significance. Yet, the results of animal testing may not fully predict the human effects.

Immunology

The evaluation of immunologic responses to silicone breast implants in humans faces significant challenges. There are large numbers of diverse immunologic responses that may be evoked in humans, whether the subjects are healthy or ill, for which the biological meaning and clinical interpretation is uncertain. Furthermore, many of the studies available for analysis are methodologically inadequate with ill-defined or inappropriate comparison subjects, unorthodox data analyses, and the potential for systematic biases in laboratory methods, exemplified by the analysis of cases and controls separately, at different time periods, by different technicians using different batches of reagents. Not surprisingly, inconsistent results in studies purporting to evaluate the same immunologic parameter are common.

While there are data showing that silicone may cause local activation of inflammatory responses, there are no consistent data to suggest systemic inflammation or systemic induction of anti-silicone or autoreactive responses in women with silicone breast implants. Immunologic responses studied include: cytokines as indicators of inflammation, natural killer cell activity, superantigen stimulation of T cells, antigen-specific T cell activation, and autoantibodies of various types (anti-nuclear antibodies, anti-collagen antibodies, and anti-microsomal antibodies), and anti-silicone antibodies. In these studies, employing different immunologic response markers, when appropriate comparisons were made, (ill women with implants compared to

healthy women with implants, or healthy women with implants compared to healthy women without implants), neither immune system activation nor autoreactivity could be reproducibly demonstrated in women with silicone breast implants. Furthermore, no unique human lymphocyte antigen haplotypes in ill women with implants have been identified. The frequency of different human lymphocyte antigen haplotypes is the same in ill women with or without implants. The main conclusion that can be drawn from existing studies is that women with silicone breast implants do not display a silicone-induced systemic abnormality in the types or functions of cells of the immune system.

In a mouse strain predisposed to the development of plasmacytomas, tumor formation was enhanced after the intraperitoneal injection of silicone gel. How this information translates to humans is currently unknown. Existing data in humans do not suggest an effect of silicone breast implants on either gammopathy or myeloma, but the number and size of studies is inadequate to produce definitive results.

Epidemiology

The evaluation of epidemiologic studies of silicone breast implants and connective tissue diseases focused on several definite connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, and dermatomysitis/polymyositis) and a grouping of less well-defined entities, which we labeled "other autoimmune/rheumatic conditions." The latter included a mixture of signs, symptoms, and diagnoses provided by the authors of the relevant studies. Several meta-analyses, which pool data from multiple studies, were conducted to identify a possible association between breast implants and connective tissue diseases.

No association was evident between breast implants and any of the individual connective tissue diseases, all definite connective diseases combined, or the other autoimmune/rheumatic conditions. Sjögren's syndrome was a possible exception to this statement. This entity requires salivary gland biopsy to meet the published diagnostic criteria. Whether biopsy was actually performed for cases in the studies cited is unknown. The remaining criteria based on dryness of the eyes and mouth with possible immunologic alterations are nonspecific and relatively common in any population group. Thus, the accuracy of diagnosis of Sjögren's syndrome in the studies incorporated in this meta-analysis is questionable.

One meta-analysis included only those studies that distinguished silicone gel-filled breast implants from any other type. The results from this meta-analysis were consistent with those from the other meta-analyses where breast implants were more broadly defined. There was no association between silicone gel-filled implants and any of the definite connective tissue diseases (including Sjögren's syndrome) or the other autoimmune/rheumatic conditions.

Rheumatology

The term *atypical connective tissue disease* has been used to describe constellations of signs, symptoms, and abnormal laboratory tests, insufficient by themselves to meet the specified criteria of a classic connective tissue disease. Among these descriptive groupings, mixed connective tissue disease and undifferentiated connective tissue disease are distinctive in that they have established case definitions, which include substantive and sustained symptoms. In most studies of breast implants, however, neither of these diagnostic entities has been evaluated as a separate disease category. Rather, they have been included in a combined grouping of ill-defined connective tissue diseases. The one study that specifically addressed undifferentiated connective tissue disease found no association with silicone breast implants. Another reported disease entity is "systemic silicone related disease," for which the case definition includes the presence of a silicone breast implant. This inclusion criterion makes scientific evaluation difficult, since there is no possibility of comparing the incidence of the syndrome in women with and without implants.

Breast implant patients have reported a diversity of symptoms and signs that are also associated with rheumatic or autoimmune diseases. For each sign or symptom showing an association with breast implants in a given study, other studies found no association. Symptoms associated with breast implants in at least one study included: arthralgias, swollen or tender lymph glands, myalgias, dryness of mouth or eyes, skin changes, and stiffness. Problems in analyzing these studies were numerous: the same complaint appeared in more than one disease category; self-report was not verified; timing of the complaint in relation to the implant was not known; indication for the implant was ignored; and in individual studies, the number of affected women was small. Furthermore, many of the rheumatologic complaints reported are common in the general population and as presenting complaints in physicians' offices. No distinctive features relating to silicone breast implants could be identified.

Little is known about the effect of silicone breast implants on clinical course and immunologic parameters in women with pre-existing classic connective tissue disease or in women who develop such a disease following an implant.

Contrary Opinions

The panel members are in agreement on the findings and interpretations of the data on silicone breast implants and connective tissue diseases, and their immunologic correlates, as presented in this report. The material presented represents an analysis of the most rigorous and relevant scientific information currently available. It is our informed opinion that the large majority of scientists in our respective disciplines would find merit in our reviews and analyses. Nevertheless, as in every field of endeavor, a few individuals may find disagreements with our statements. As individual scientists and as a group, we have taken no predetermined position on the issues, nor have we designed the report to refute or enhance any point of view. On the contrary, we have allowed the existing research data to lead us to the conclusions presented. We cannot anticipate what research findings may appear in the future.