Will The Real Junk Science Stand Up? An Analysis Of The Mayo Clinic Womens Study And Harvard/Brigham Nurses Study In Relation To The Silicone Gel Breast Implant Controversy

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Body

In recent months there has been much publicity in the press about two epidemiology studies published in The New England Journal of Medicine: (1) the 1994 Mayo Clinic study, entitled ″Risk of Connective Tissue Diseases and Other Disorders After Breast Implantation,″ by Sherine E. Gabriel, M.D., et al., and (2) the 1995 Harvard, Brigham & Womens Hospital Nurses Study by Jorge Sanchez-Guerrero, M.D. et al. entitled ″Silicone Breast Implants and the Risk of Connective Tissue Diseases and Symptoms.″

The breast implant manufacturers and even the leadership of the American College of Rheumatology are claiming that these studies confirm with scientific certainty that silicone gel breast implants do not cause connective-tissue disease or in fact any disease. Dow Corning has been running full-page ads in The New York Times and The Wall Street Journal trumpeting this claim. As recently as October 13, 1995, on The Oprah Winfrey Show, the CEO of Dow again repeated these claims.

In my view a hoax has been perpetrated on the public by Dowand the authors of these studies that if not stopped will cause significant damages to women who trust this flawed science and believe mistakenly that their implants are safe.

The facts are that these studies never should have been published. The studies are worthless ″junk science″ -- except to those who use their publication and the imprimatur of their institutional supporters and publishers (the Mayo Clinic, Harvard Medical School and The New England Journal of Medicine) to further the false claims that breast implants do not cause disease.

No doubt it was with the Daubert decision in mind that Dow Corning and other breast implant manufacturers sought to obtain peer-reviewed medical literature to support their legal defense. What could be better than studies done by the Mayo Clinic and Harvard Medical School affiliates published in The New England Journal of Medicine?

Reasonable analysis of the studies compel the conclusion that Daubert offers no protection from those willing to buy science to support their positions. Daubert may well be limiting a jury's right to evaluate all evidence and aiding those with money and power who are able to buy admissible evidence necessary to support their position under the Daubert standard.

Dr. Charles H. Hennekens, Professor of Epidemiology at Harvard University's School of Public Health stated on October 7, 1995, ″Epidemiology is a crude and inexact science . . . . We tend to overstate findings, either because we want attention or more grant money.″ Dr. Hennekens is the epidemiologist in charge of the womens' health study at Harvard. In analyzing the Mayo Clinic study and the Harvard Nurses Study, Dr. Hennekens' statement is most appropriate.

The Mayo study purports to follow and compare 749 women with breast implants for a mean average of 7.3 years and 1,498 women controls without implants for a mean average of 8.3 years. The study claims ″in 5 case subjects (with breast implants) as compared with 10 subjects in the control group, one of the specified connective tissue diseases

was diagnosed." As the result of this comparison, the authors "found no association between breast implants and the connective tissue disease and other disorders that were studied." In fact, one might conclude from the study conclusion that implants improve one's health. However, if you examine the Mayo study carefully, you are compelled to conclude the study may in fact confirm a causative connection between breast implants and the defined connective tissue diseases studied (exactly the opposite of the authors claim).

The Mayo authors claim that they "followed' 749 breast implantwomen for a mean of 7.3 years is, in fact, a misleading statement at best, and in my opinion, a totally false representation!

Follow-up, according to the authors, was to "December 31, 1991 or the date of the womens' last health care visit in the county" (whichever was earlier not later). Thus, all women with breast implants who received their implants at Mayo between January 1, 1964, and December 21, 1991, were included in the study. If a woman received her implants for example on January 1, 1964, and moved from the county in 1965, or had no further care under the Mayo system because she went elsewhere, no effort was made to contact her, send her a questionnaire or examine her subsequent medical records or in fact examine any medical records other than the Mayo's records. From the date of her last visit at Mayo she was treated as "healthy" or needing or receiving no medical care! The authors would not even know if the patient died if she did not die at Mayo.

The authors should have stated that they did no follow-up of women who left the Mayo health system for any reason whatsoever, such as moving, treatment outside the system, etc. The authors' claim that they "followed" the case of these women in the study is simply not true.

The control group the authors used was not a normal group of women. It was, in fact, patients of the Mayo Clinic. Thus, one would expect a bias towards diseases in the control group. This isconfirmed by the fact that 3 of the 10 women with "connective"tissue disease in the non breast implant control group had ankylosing spondylitis, an extremely rare, genetically-related disease in women that is not a connective-tissue disease. Why were these 3 women included in the control? Had this non connective-tissue disease group of 3 women not been included it appears the authors would have to conclude the study confirmed an association between breast implants and the connective-tissue diseases studied.

The authors' claim "that contrary to previous reports, the incidence of abnormal test results for antinuclear antibodies (ANA, the test for Lupus) in women with breast implants did not differ significantly from the incidence in women without implants" is false. There was no follow-up of the implant patients; the authors have no idea how many had or did not have ANA tests.

The known latency period before developing rheumatological complaints in patients with implants was not appropriately considered. Silicone, like asbestos and tobacco, has a long latency period -- often 7 to 15 years or longer. The authors claim only 36% of the cases with implants had been "followed" for 10 years. Even this number is suspect because the authors have no basis to claim these women continued their medical care at Mayo. One would expect that the earlier the date of the implant, the less chance the recipient was still under the Mayo health system. The claim "our controlled study allowed extensive follow-up of a population based cohort of women with silicone containing breast implants and the corresponding control group" cannot be substantiated by the authors. The authors made no effort to determine how many women in their study resided in the county after their implants were received, how long they resided or even how many continued to receive care at Mayo. The reader was allowed to make the false assumption the women studied were continuing patients treated at Mayo.

The Mayo authors appear to have intentionally distorted their conclusions by conceding some obvious weakness in terms of numbers of participants, not examining the participants and limiting their study to review only medical records of the Mayo Clinic.

The authors claim that the Mayo study was funded in part by the Plastic Surgery Education Foundation of the American Society of Plastic and Reconstructive Surgeons (PSEF). In fact, that statement is misleading at best. Dow and other manufacturers gave PSEF money. PSEF, in turn, funnelled the Dow money to Mayo. (See deposition of R. Barrett Noone, M.D., Chairman of the PSEF where he states that PSEF was the "facilitator" to deliver the manufacturers' money, taken September 7th and 9th, 1994 in MDL 926 by me). Mayo is aware of this yet refuses to disclose the true source of their funds.

The Mayo researchers did not disclose that initially 971 medical records of women with breast implants received from Mayo were included in the study. Initially they excluded 149 because of not meeting criteria, without noting what the criteria were they did not meet. The Mayo researchers then advised PSEF that 822 breast implant cases remained in the study yet the publication in The New England Journal of Medicine refers to only 749 women. What happened to the 73 women with breast implants who met the criteria but do not appear to be mentioned in the study? Did they have diseases and therefore were they excluded because the authors were trying to help their financiers? We may never know.

The Mayo researchers did not disclose that the Mayo Foundation is a defendant in silicone gel breast implant cases and was so at the time that this article was published. At least one case I know of where they are a defendant is Conway v. The Mayo Foundation, et al. in the State of Minnesota, County of Ramsey, No. C5-93-12012. Why was this information not disclosed in the article?

The Harvard authors did not look for the atypical diseases that the treating doctors believe are associated with implants but instead looked only at narrowly-defined, classical connective-tissue diseases. A similar problem exists with the Mayo study except they added a non-connective-tissue disease, ankylosing spondylitis, to their control.

The Harvard sample is too small. The study has almost no statistical power in terms of numbers to detect an association with the autoimmune diseases studied. The same problem is true of the Mayo study.

The study design is problematic. The authors attempt to make it appear that they made a realistic attempt to separate their study into two groups: (1) a ″definite connective tissue disease″ group and (2) a ″connective tissue disease based on less stringent criteria″ group.

In the less stringent group, according to the authors, were ″women with possible early, milder or atypical forms of connective tissue disease or with any signs or symptoms of a connective tissue disease who did not meet standard classification criteria.″

From this statement it sounds as if the authors werelegitimately trying to study the atypical disease that a substantial number of rheumatologists, internists and immunologists argue that breast implants cause. This statement by the authors is misleading at best, for that was not the disease process they were studying or intended to study.

In order to enter the ″less stringent diagnostic criteria″ category it appears that the women would have to achieve the following criteria. (Mind you nowhere do the authors specify clearly the criteria. On must piece this together from reading the study numerous times and even then it is unclear.)

The nurse must have reported a rheumatic musculoskeletal or connective-tissue disease on questionnaires sent to her before January 1, 1990 and also answered a screening questionnaire sent to her in 1992 asking her if she had any of ″41 signs or symptoms or laboratory findings in connective tissue disease.″ In fact only 32 of the women were sent the screening questionnaires. Thus, the screening questionnaire was of no value since only 32 of the nurses were sent questionnaires. Of course, that is 32 more than were sent questionnaires in the Mayo study (non were sent).

It would appear that even if a diagnosis was made before June 1, 1990, any nurse who did not disclose that diagnosis until the 1992 questionnaire was excluded and considered healthy. In addition, if the diagnosis was after June 1, 1990, they were also excluded.

It would appear that the Harvard/Brigham researchers asked specific questions about Lupus in the 1982, 1984 and 1986 questionnaires and about rheumatoid arthritis through the 1992 questionnaire. Before 1992, the authors did not include questions about scleroderma, polymyositis, dermatomyositis and Sjogren's syndrome. Thus, a nurse who although having those disease before June 1, 1990, but had not mentioned having these diseases on a previous questionnaire was not sent a screening questionnaire.

Apparently, the only other way a woman received the screening questionnaire was if she had answered a 1990 or earlier question stating she had had ″other major illness diagnosed″ with an answer of ″rheumatoid arthritis, scleroderma, morphea, systemic Lupus erythematosus, dermatomyositis or polymyositis, Sjogren's syndrome, connective-tissue disease not further specified or any arthritis, excluding osteoarthritis and fibromyalgia.″ I presume

diseases that the nurse did not consider a ″major″ illness were not to be listed in answer to the question. If a nurse believed Sjogren's syndrome was not a ″major″ illness then she was out of the study even if she had the disease in 1988 and did not indicate it until 1992. It would appear that if a woman had an early, milder or non-major illness, or atypical forms of connective-tissue disease, she would have no chance of being in the screening study unless by sheer luck she considered her problem a ″major″ illness and so answered the questionnaire by 1990.

This flawed study design may explain why only 1% of this middle- aged group of women ″had any of the '41 signs or symptoms' or laboratory symptoms or laboratory findings seen in connective-tissue disease.″ I believe any competent rheumatologist would agree this is an unbelievable statistic: Raynaud's, one of the 41 criteria being investigated, is present in 5% of the general population alone. In addition, no disclosure was made of how many of these nurses had ever been tested or examined for any of these ″41 signs, symptoms or laboratory symptoms or findings″ and if so, which ones, or even if they were asked that question. There apparently was not even a reasonable effort made by the authors to find out how many had been tested for these 41 items even in a limited analysis of a few participants in a separate cohort. Obviously, if the nurse had never been tested or examined for these 41 objective items she could not answer the questions on the screening questionnaire with any relevant information.

To meet the more stringent category of ″Definitive Connective Tissue Disease,″ the nurses needed all of the above plus agreement of two rheumatologists from apparently Brigham and Harvard that their disease was not early, mild or atypical and met the standard criteria for the disease.

To make the study design appear more credible the authors requested medical records for 67 women by random sample. The researchers did not confirm one of the most important concerns of the study -- whether there was accurate reporting or non-reporting of disease. If disease reporting or non-reporting was analyzed and validated by this ″blind″ review it is not reported by the authors surprisingly in their publication.

The Harvard study claimed that one woman studied had silicone breast implants for 40.5 years and another had silicone implants for 37.5 years. This is impossible as the first implants hit the market in 1962. The study ended in 1990. The longest any woman could have had her implants is 28 years. On the flip side, the Harvard researchers also included women who had implants in for as little as 30 days.

Although the study does an admirable job of disguising its flaws, it is submitted that it is so grossly flawed as to be inexcusable that the New England Journal permitted its publication and tax payers' money was wasted on it.

The Harvard authors, by their own admission, refused to analyze the study answers of ″fibromyalgia″ because they said the disease was too ″subjective,″ even though nurses were diagnosed with that disease and answered that it was a ″major″ illness and diagnosed before June 1, 1990 (even as a separate cohort). Certainly this was at a time even the authors must concede ″bias″ (other than perhaps the authors' interpretation of the answer) could not have been a factor in influencing the nurses' answers. Sending these women a questionnaire on the ″41 signs, symptoms,″ would perhaps produce some information. In fact, fibromyalgia combined with certain of the ″41 signs, symptoms,″ appears much more like the atypical disease that is related to implants than to any other diseases the authors studied.

The Harvard authors collected data through 1992 but only reported on data up to June 1, 1990. Why didn't the authors include data for those nurses meeting their strictly defined disease criteria after June 1, 1990, in at least a separate cohort, instead of just dismissing the information as not being worth publishing because of ″bias″ created by the ″breast implant controversy.″ This sounds much like the pot calling the kettle black. Using this logic, the entire Harvard study should be tossed because of the pro-Dow bias that the authors have so clearly demonstrated. The authors strangely have great concern for every one's bias except their own.

Our information is that as of 1995 Dow has paid over $7 million dollars to Brigham. Dow and the other breast implant manufacturers paid consulting fees to Harvard study authors and manuscript reviewers, including Drs. Matthew Liang and Peter Schur. Others such as Dr. Graham Colditz and J. Sanchez-Guerrero, other Harvard study authors, severed as experts in litigation on behalf of the manufacturers. The full amount of these payments and nature of the relationship has never been fully disclosed in the literature or to the public at any time. Why? Some short months after Dow Corning made a $1.2 million payment to Brigham/Harvard, Professor Schur of Brigham, also the editor of Arthritis and Rheumatism, invited the president of Dow Corning to submit a ″position statement″ for his journal.

Schur claims to have sought approval to publish the ″position statement″ of associate editors, Drs. Matthew Liang, who co-authored the Harvard study, and Don Goldenberg, both Harvard faculty and both paid consultants for breast implant manufacturers. Schur never sought approval or advice of his ″Publications Committee″ before the ″position paper″ was published. Publication of such a ″position statement″ is virtually unheard of in this journal and was strongly objected to by the publication committee chairman, who only learned of the publication after it was published. At the same time as the ″position statement″ was solicited, Drs. Schur, Liang and Guerrero wrote an article for Arthritis and Rheumatism that concluded that the epidemiologic evidence to date did not support the claim that breast implants could cause connective-tissue disease.

This article and Dow's ″position statement″ were published in the February 1994 issue of Arthritis and Rheumatism. There was no disclosure of the payments by breast implant manufacturers to the authors, or to Brigham. There was no disclosure that Drs. Schur, Liang and Goldenberg were consultants for the manufacturers when the article was written and published.

The editors of Arthritis and Rheumatism, including Schur, Liang and Goldenberg, refused to permit publication of any article claiming a causative connection exists between breast implants and any disease or complication, despite the fact that several were submitted for publication by highly respected scientists and authors.

While Dr. Peter Schur was not listed as an author of the Harvard study published in The New England Journal of Medicine in June of 1995, he is thanked at the end of the study in small print for his help. No disclosure was made of the substantial payments he recieved from breast implant manufacturers or the fact that $7 million was paid by Dow to Brigham. Was this done in order to hide from the public the full involvement of Dow and the breast implant manufacturers with Brigham and certain of their faculty?

No disclosure was made in the Harvard study that in the preliminary findings of a much larger ongoing study at Brigham (in which 200,000 women had already answered questionnaires by August 1993) that researchers had found a 45-59% increased risk of rheumatoid arthritis in women with breast implants. This information was in direct conflict with the Harvard/Brigham study although the research was being done at Harvard/Brigham and the information was known to the authors. No disclosure to the public of this information has to date been made by Brigham. This information is now being made public through other sources.

In the May 1995 issue of Arthritis and Rheumatism, in response to criticism from several highly-regarded physicians and scientists that Drs. Schur, Liang and Guerrero's publications ″misrepresent the majority of clinical and immunologic findings to date,″ Schur, Liang and Guerrero and co-author John S. Sergent of Vanderbilt cavalierly dismissed important scientific facts and demonstrated their total and complete bias in a response letter in which they:

dismiss the fact that silicone is a potent adjuvant, claiming it must be ″thoroughly homogenized with antigen in vitro to have an adjuvant effect. This would not be expected in the human situation,″ a ludicrous position at best.

dismissed histochemistry (blood work) findings stating that ″histochemistry findings are remote evidence for systemic effects″ to be considered as relevant, another ludicrous position.

dismissed evidence of substantial improvement after explantation as likely to ″be a strong publication bias″ and therefore irrelevant.

dismissed studies looking into whether breast implants cause a ″unique disease″ because, as they stated, ″given the high prevalence of fibromyalgia and other subjective symptoms described and the current litigation environment, proving such a relationship would be a formidable task indeed.″

dismissed manifestations of disease such as ″arthralgias, myalgias, cognitive dysfunction and fatigue″ as not being ″objective physical evidence″ and therefore not worthy of consideration in their investigations.

The New England Journal of Medicine editors state in the Harvard study that the ″disclosure statement is in accord with our usual policy but is somewhat more detailed because of the intense public controversy over the health effects of breast implants.″ I submit their disclosure policy is sadly lacking regarding any meaningful disclosure requirement.

Why do the Brigham researchers keep using the claims that 1 million to 2.2 million implants are in womens' breasts in the United States when in fact they know that Dow Corning investigators on December 12, 1990 stated:

″U.S. projection of implant breast devices in the U.S. is 544,000. Note: This translates to 4.2 per 1,000 adult women with breast implants for any reason. In Approximately 320,000 women, 25.9% of the devices have had some type of problem associated with them. Note: This translates to 30.3% of the women with some type of problem.″

Was the reason to not fully disclose this information, and at minimum publish their findings in at least a separate cohort, aimed at assisting the manufacturers' position? Wouldn't using accurate information change the epidemiologic study criteria and their findings?

Was there disclosure to the National Institutes of Health (NIH), from whom grants were received, that some of the Harvard study researchers were paid consultants and experts for the breast implant manufacturers? If so, were the disclosures made to NIH before the studies were published? Was the NIH aware that Dow Corning had paid over $7 million to Brigham? If so, to whom and how were these disclosures made?

The authors of the Harvard study need to explain how in March of 1992 Dow Corning had in its possession a copy of the Harvard study questionnaire, months before the questionnaire was sent out to the nurses. Were the questions changed after that date and if so, why? Certainly no scientist I know of who supports a causative connection to disease has a copy of the questionnaire even now. Several requests for the questionnaire have been made and refused.

Conclusion There are many excellent scientific studies that support the causative connection of breast implants to disease. Unfortunately, these scientists do not have a public relations machine like Dow to publicize them. Nor have they the financing of major corporations who support them and pay to publicize their findings. Space does not permit a discussion of them. Unfortunately, unless we find a way to stop large corporations from buying favorable scientific results and control scientists who tend, in Dr. Hennekens' words, to ″overstate findings because they want attention or more grant money,″ we won't be able to trust the integrity of ″scientific″ conclusions. The jury system without Daubert sanitization ″protections″ may be one of the best answers to protect the public from this conduct.

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