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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. clipping	re: fax number (partial) (1 page)	09/18/1997	P6/b(6)
002. report	re: Atypical Rheumatic Diseases (partial) (3 pages)	04/17/1997	P6/b(6)
003. report	re: National Board Meeting (partial) (2 pages)	04/13/1997	P6/b(6)
004. report	re: Internal Dow Corning study (18 pages)	05/17/1978	P4/b(4)
005. report	re: Dow Corning study (6 pages)	05/29/1980	P4/b(4)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Devorah Adler
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FOLDER TITLE:
[Silicone Breast Implants] [Binder] [2]

2012-0463-S
rc824

RESTRICTION CODES

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A Tribune Publishing Company
435 N. Michigan Ave., Chicago, Ill. 60611

...nesday, September 17, 1997

Silicone implants don't cause breast cancer, U.S. says

From Tribune News Services

WASHINGTON—Silicone breast implants do not cause breast cancer and there is only "borderline" evidence linking the devices to any other disease, according to a federal review of scores of medical studies.

The review even pointed to a possibility that implants could help protect against breast cancer, but researchers said more studies were needed to draw a conclusion.

A report to be published Wednesday in the Journal of the National Cancer Institute gives silicone breast implants a "clean bill of health" so far as cancer and other disease is concerned. Researchers did find that the devices frequently break and that escaped silicone spreads throughout the body.

S. Lori Brown of the Food and Drug Administration, a co-author of the review, said there is some slight statistical suggestion linking some types of connective tissue disease to leaking breast implants, but she called it "a borderline result" that should be interpreted "very cautiously."

"These diseases are so rare that it may never be possible to clearly link them to silicone breast implants," said Brown.

The conclusion of the research review contrasts starkly with the statements in lawsuits by thousands of women who link silicone breast implants to a wide variety of diseases. About 300,000 women have settled lawsuits with manufacturers of the implants and about a half-million others have reserved the right to sue. Thousands of suits are pending.

Some manufacturers are offering fixed settlements that range from $5,000 to $100,000 for women whose implants have ruptured. Manufacturers have won 16 of 21 lawsuits that have gone to trial and jury awards have ranged from $30,000 and up. A Houston woman originally was awarded $25 million, but she settled later for an undisclosed amount.

Silicone implants were introduced in 1962 to augment breast size or for reconstruction after a cancerous breast was removed. Between 800,000 and 1 million women received the implants, many for cosmetic purposes. After reports began surfacing about implant breakage and possible health effects, the FDA in 1992 restricted their use.

Since then, said Brown, about 14,000 women have received implants.

Brown and Louise Brinton of the National Cancer Institute evaluated more than 100 studies on the medical effects of silicone breast implants and gave the devices a clean bill of health.

"We found that, if anything, implants may actually decrease the risk of breast cancer," said Brown. "The studies are quite consistent in finding a decrease. It is not clear what is causing that decrease, if it is real."

The researchers said it is clear that breast implants do break, allowing silicone to escape into the body. They said studies of removed implants found that 23 percent to 64 percent had some type of tear or rupture.

Brown said women also experience side effects from implants: pain caused by the shrinkage of internal scar tissue, and body form distortions caused by breakage of the implant envelope.

She said there is anecdotal evidence linking escaped silicone to multiple myeloma, a type of cancer, and to other diseases, but no proof has been published.

Brinton said that a 15-year study of 13,500 women who received implants is being evaluated. It is the largest study yet attempted. Results are expected in about a year.

AP Corrects Breast Implant Story

APO 9/19/97 1:28 AM

WASHINGTON (AP) -- In a Sept. 17 story on silicone breast implants, The Associated Press incorrectly reported that researchers had given the implants a clean bill of health regarding diseases other than breast cancer.

Food and Drug Administration scientist S. Lori Brown did say the review of previously published studies found no indication the implants were linked to breast cancer. But she said researchers had found some slight statistical evidence linking the implants to some types of connective tissue disease, and said those findings needed further study.

The cancer findings were part of a published paper; the findings regarding other diseases were not published but Brown discussed them in an interview.

KATHLEEN W. ANNEKEN, R.N. &
SYBIL NIDEN GOLDRICH,
Co-founders

For Immediate Release
September 16, 1997

Contact: Linda Ricci
Karin Wallestad
Fenton Communications
202-822-5200

RESPONSE BY COMMAND TRUST NETWORK TO NCI STUDY ON SILICONE BREAST IMPLANTS

Sept 16, 1997 -- Silicone implants bleed, rupture, and cause silicone to spread throughout a woman's body, a published National Cancer Institute review confirms today.

The study's authors conclude that the silicone breast implants do not increase the risk of breast cancer. The Command Trust Network of silicone breast implant survivors has never claimed that they did.

However, the study cites "experimental data" to "support the need for further evaluation of sarcomas" and other cancers "particularly multiple myeloma." We at Command Trust Network have been aware of the inconclusive but growing evidence on multiple myeloma and welcome National Cancer Institute's call for further study of this issue.

Today's Associated Press wire story is erroneous in saying that the study gives silicone breast implants "a clean bill of health so far as cancer and other disease is concerned." In fact, the study says no such thing about other diseases. It is concerned purely with cancer. In mentioning the evidence for other disease the study in fact acknowledges that "[t]he issue of an atypical disorder or syndrome related to silicone breast implants has not been resolved." We at Command Trust Network have long maintained that the leaking silicone is contributing to a new, atypical disease, as indicated in the recent Dow-funded University of Michigan study.

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Beverly Hills, California 90212

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April 17, 1997
Atypical Rheumatic Diseases and Silicone Breast Implants Workshop
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health (NIH)
Bethesda, Maryland

Upon FDA invitation, Pamela Stott-Kendall, author of *Torn Illusions*, and Diane Griffith, congressional liaison of USSW, attended a decisive, NIH-sponsored convening of nineteen medical specialists who met to discuss atypical rheumatic diseases in association with silicone breast implantation. (Unfortunately, Marlene Keeling of Houston, Texas, had returned home and was unable to join us.)

Limited to "atypical rheumatic disease" discussion, the Workshop was divided into two panel-groups for scheduled, morning and afternoon programs. The morning segment's panel-seating of speakers was comprised of rheumatologists, epidemiologists (two were associated with industry-funded research projects), one plastic surgeon (industry-consultant Dr. Garry Brody), FDA representatives and NIH cancer-researcher Dr. Michael Potter. Though the presentations given by each member of this speaker-group reflected the opinions and positions of both industry and independent researchers, there seemed to be somewhat of an equal balance.

Supporting the occurrence of breast implant-related, atypical connective-tissue disease (CTD), Dr. Gary Solomon (Director of Rheumatology Clinic, Hospital for Joint Diseases and Associate Director, Department of Rheumatic Diseases, Hospital for Joint Diseases Orthopedic Diseases, New York)) and Dr. Stuart Silverman (Professor of Medicine, Director of Women's Bone Health Program, Veteran's Administration, Los Angeles, and Medical Director, Osteoporosis Medical Center, Beverly Hills, California) jointly presented compelling evidence (both clinical and serologic) of unique, atypical CTD occurring in large numbers of silicone breast-implant patients. Dr. Solomon and Dr. Silverman made note of silica's inclusion, cytokine (IL-2) production, neurological abnormalitics—such as neuropathy, ataxia, muscular weakness and neuro-cognitive deficits with attention-deficit disorder—and chronic fatigue and fibromyalgia findings that do not conform to established disease-criteria of classical CTD and may reflect a "genetically-mediated response to chemicals." It was suggested that "cytokines may play a role" in this atypical illness, which is "dose and time related." The patient registry of National Cancer Institute's Dr. Rabkin—reporting eighteen cases of myeloma in breast implant patients—was also discussed. (Myeloma is a rare form of cancer associated with monoclonal gammopathy; most frequently reported in men over the age of fifty, it is now reported in younger women, under forty-five years of age, with breast implants.) Not mentioned were findings and documentation of implant-associated demylinating disease and silicone allergy. For example, the published research of Dr. Ira Finegold, President of the American College of Allergy and Immunology, cites a 26 percent occurrence of allergy to Dow Corning's silicone gel. (Reference: "Allergy to silicone, is it real?," *Comprehensive Therapy*, 22, June, 1996.)

Representing the National Institutes of Health, Dr. Michael Potter (Chief, Laboratory of Genetics, National Cancer Institute, NIH) presented the results of research pertaining to plasmacytoma and silicone granulomas. He stated that myeloma in implant patients "should be

followed and studied' and that implants are "immunological agents." However, he did not discuss one of his published NIH studies, entitled "Cytotoxicity and membrane damage *in vitro* by inclusion complexes between *y*-cyclodextrin and siloxanes." The findings of this study reported that "low molecular weight siloxanes produce lethal effects on B-lymphocytes derived target cells *in vitro* and permeabilize the plasma membrane in lower sublethal concentrations."

FDA speakers were Dr. Kimber Richter (Deputy Director for Clinical and Review Policy, Office of Device Evaluation, FDA Center for Devices and Radiological Health) and Dr. Frederick W. Miller (Senior Investigator, Laboratory of Developmental and Molecular Immunology, FDA Center for Biologics, Evaluation and Research). Regarding the high rate of rupture, FDA's Dr. Richter stated: "We see a sixty-four percent rupture rate." She described gel-bleed as occurring in "virtually all implants" and also discussed the largest study of explants yet conducted. Authored by Dr. Robinson, the explant study confirmed: the shedding of silicone from outer implant-shells; folds in outer implant-shells, which contribute to rupture, in 55 percent of explants; strength tests showing weakness of outer implant-shells with age; and variations in thickness of gel and shell found in different implant products. Relating to rupture detection, Dr. Richter said that "it's difficult to determine if an implant has ruptured." She also reported on the latest findings of the "new" Mayo study which cites high re-operation rates following breast implantation and higher complication rates in mastectomy patients than in cosmetic patients. The focus of Dr. Miller's presentation centered upon the unusual, atypical CTD findings reported in myositis patients with breast implants. (Myositis is an inflammatory, progressive disease of an involuntary muscle.) Dr. Miller stated that myositis patients with breast implants "differ in certain clinical, serological and immunological features." Dr. Miller discussed the neuro-cognitive deficits that are also associated with myositis in breast implant patients and that are not commonly associated with the traditional form of disease. During a panel question and answer period, one panel member suggested that these neuro-cognitive deficits, now well-reported in breast implant patients, might be a factor influencing the results of self-report research studies—like the industry-funded Mayo and Harvard research projects. (Research presented to an earlier March, 1995 Immunology of Silicones Workshop, sponsored by the National Institutes of Health, had reported breast implant-related "neuro-cognitive deficits consistent with chronic solvent exposure."

Industry consultant Dr. Garry Brody (Clinical Professor of Surgery, Division of Plastic Surgery, University of Southern California, Los Angeles) presented facts on gel and shell make-up. Dr. H. James Williams (Chief, Division of Rheumatology, Department of Internal Medicine, University of Utah, School of Medicine, Salt Lake City) reviewed classifications of rheumatology. On epidemiology report, Dr. Dr. I-Min Lee (Assistant Professor of Medicine, Department of Epidemiology, Harvard School of Medicine, Boston) discussed the findings of Harvard's study which cited a significant, 24 percent increase of CTD in the small number (3%) of breast implant patients included in the Harvard project. However, Dr. Lee neglected to mention that an unpublished part of this study, which recently surfaced, had reported, significantly, a 59 percent increase of rheumatoid arthritis in these same, breast implant patients. Dr. Maureen Mayes (Associate Professor of Medicine, Division o Rheumatology, Wayne State University, Detroit, Michigan) reported on the "old" Mayo study. Dr. Mayes' presentation did not give notice of the abstract findings of her authored, Wayne State University (Dow Corning-funded) research, which initially found that "the presence of implanted devices, particularly those containing silicone, increase the risk of developing UCTD [undifferentiated connective-tissue disease].

For some unknown reason, these findings are in the process of being reassessed before public release. I suspect that Dow Corning was not pleased with the original study-findings.

After a lunch-break, the afternoon program was comprised of a panel seating of selected medical "experts," without special-interest affiliation, who conducted a discussion of the morning presentations. Three questions were directed to this panel:

"1. Given the current information, is there reason to believe that atypical forms of rheumatic diseases can be defined?

2. Given the current information, is there reason to believe that a possible association may exist between atypical CTD and silicone breast implants?

3. Are there other questions that should be addressed on this topic? or What, if any questions, should be addressed to this topic?"

In answer of the first question, Dr. Solomon and Dr. Silverman presented the panel with suggested, appropriate disease criteria in definition and classification of the atypical CTD reported in women with breast implants. Listed exclusions were: 1) local or metastic cancer; 2) exposure to chemicals already known to cause CTD; and 3) chronic infection prior to implantation. Some of the major criteria listings included symmetrical myalgia (four to ten tender points), chronic fatigue, cognitive deficits and objective sicca complex. Some of the suggested, minor criteria were listed as local disease, arthalgia, frozen shoulder, subjective sicca, non-scarring alopecia, Raynaud's syndrome, photosensitivity and positive ANA.

Regarding the second question as to a possible association between atypical CTD and silicone breasts implants, the general panel-consensus, was, based upon the Workshop presentations, "yes." One expert panel member, remarked that, although entering the Workshop a "skeptic," she would now have to say a possible association does exist. NIH researcher Dr. Potter stated that the data and information presented "calls for unbiased study" of a type that NIH was able to conduct. As time was running short, the third question did not draw a great deal of discussion.

Overall, I believe that the April 17 Workshop signals an important, scientific turn towards acknowledgment of silicone breast implant-related disease as well as its uniqueness, its call for definition, classification and, above all, research study. However, atypical CTD is merely one facet of silicone-associated disease, which systemically affects the body as a whole. Other medical specialties—such as toxicology, neurology, endocrinology, oncology, allergy and pediatrics—should participate in group discussions of appropriate disease-criteria for classification and design of future research study. Just as critical, currently-ill breast implant patients must be part of any study effort.

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April 13, 1997 Address
National Board Meeting
National Organization for Women (NOW)
Washington, DC

Patricia Ireland, President of the National Organization for Women, kindly extended to us an invitation to speak during the Public Policy segment of a National Board Summit, on April 13, 1997, held in conjunction with the organization's Washington Convention of Young Feminists. Our group presented a Board summary of recent congressional and governmental appointments, and results, regarding our March 18 *Letter to Congress: a Statement of Legislative and Governmental Relief for Silicone Implant Recipients.*

Basis for Text of Address:

"We would like to thank you for this opportunity to congratulate the National Organization for Women on its early recognition, as well as support, of our rapidly-enlarging, silicone health-crisis—one affecting, in particular, today's young generation of women. Still unaware and not warned of silicone's dangerous risks and the devices' experimental status, another seventy to eighty-thousand women, many of whom are quite young and are at child-bearing age, continue to undergo breast implantation each and every year. In the meantime, implant manufacturers continue, each and every month, to report to the FDA, through the mandatory Manufacturer Device Reporting (MDR) program, several thousand new cases of breast-implant related injuries and illnesses, and several new reports of documented death. Yet according to research presented to the National Institute of Health, only 300,000 of some two million breast-implanted, American women have reached the period of high risk; the FDA acknowledges a seven to fifteen-year period of latency before symptoms surface and implant-associated illness strikes. As even more of these women steadily die and increasing numbers of other women, including their children, suffer devastating toxic-effects and related disease—while the industry manages to escape financial responsibility and health-insurance providers deny coverage for silicone-related, medical care—the need of governmental and legislative relief has become critical.

In seeking this relief, our time in Washington has been productive. Beginning with a February 26 FDA meeting of Center for Devices and Radiological Health scientists in action on a Citizen Petition, filed by CANDO of Texas, to permanently ban silicone breast implants, and a USSW-sponsored, February 24 Congressional Briefing on Dr. Arthur Brauer's latest silicone research soon to be published, we returned to Washington for additional appointments with governmental and congressional leaders.

On April 4, we met with Deputy Director Anne Bavier and Dr. Vivian Pinn, Director, of the Office of Research on Women's Issues, National Institutes of Health (NIH), to discuss future, silicone-research projects. It was our suggestion to NIH that currently-ill women (excluded from manufacture-funded research) must be studied. We have spoken with Chief Judge Samuel Pointer, MDL 926, Birmingham, Alabama, to explore the possibility of using the submitted and

approved medical records of current claimants, totaling approximately 100,000 of 450,000 Settlement participants.

We have also met, on April 10, with officials of the Bureau of Consumer Protection, Federal Trade Commission (FTC), in an effort to initiate an investigation of false and misleading breast-implant advertisement, most of which is seemingly geared to lure and entice very young, and impressionable, women. Officials of the Bureau of Consumer Protection have agreed to contact the FDA Commissioner Special Assistant for Investigation to obtain other evidence of fraudulent advertisement already submitted to the FDA by our group, on February 26, during the earlier Washington, DC, visit.

In response to a request for Presidential appointment of a Federal Task Force (described in the March 18 *Letter to Congress*), our group attended a White House meeting with Mary Dixon of the White House Office for Women. After our presentation, Ms. Dixon asked for a few days to review all of our submissions and scheduled a return appointment for us on Monday, April 14, to discuss possible plans of action in greater detail.

In gathering congressional and senate support of goals set forth in the *Letter to Congress*, prepared for the National Organization of Women, we have attained preliminary interest in pursuing the issue of a senate version of the Breast Implant Accountability Act, a House bill introduced by Representative James Traficant and which has been signed by 26 House members. This consideration comes from Florida's Senator Graham. Consideration has also been obtained from Congressman Tim Roemer's office, responsible for a congressional bipartisan petition that pressured the FTC into reopening an investigation of tobacco ads run by R. J. Reynolds. Known as the "Joe Camel" ads, these advertisements were seen as ones targeting young children. Congressman Roemer's Senior Legislative Assistant has agreed to begin looking into the documentation of our complaint that breast implant advertisement, on many fronts, is false and misleading. There is a possibility that a similar, congressional bipartisan petition—calling for FTC investigation of breast implant advertisement—might be forthcoming.

Much has been, and is being, accomplished through the presentation and diligent follow-up of our statement of necessary legislative and governmental relief for silicone implant recipients. But we also feel that NOW's support of the *Letter to Congress* is urgent and crucial to achieve necessary impact on a larger scale. On behalf of so many unfortunate women, we thank your for your continued support.

SUMMARY OF THE ATYPICAL RHEUMATIC DISEASES AND SILICONE BREAST IMPLANTS WORKSHOP
April 17, 1997

BACKGROUND:

Several studies have addressed the possible health impact of breast implants. The conclusion of these studies is that there is no association between implants and well-defined rheumatic disease -- such as rheumatoid arthritis, lupus erythematosus, or scleroderma. Nevertheless, there is a lingering question as to whether there is an association between silicone breast implants and an atypical form of rheumatic disease. Because of its concern about this issue, the National Institute of Arthritis and Musculoskeletal and Skin Diseases organized a scientific workshop on April 17, 1997, to examine and discuss the available data on a potential association in the context of current knowledge on immunology, rheumatology, and epidemiology.

A group of scientists and clinicians who had not yet formulated an opinion on this issue heard presentations from a number of scientists about their experience with atypical rheumatic disease. They also learned about issues related to silicone breast implants.

QUESTIONS ADDRESSED:

(1) Given the current information, is there reason to believe that atypical forms of rheumatic diseases can be defined?

(2) Given the current information, is there reason to believe that a possible association may exist between atypical connective tissue disease and silicone breast implants?

(3) Are there other questions that should be addressed on this topic? or What, if any questions should be addressed to this topic?

PARTICIPANTS:

A wide range of experts, including rheumatologists, immunologists, epidemiologists, plastic surgeons, dermatologists, basic scientists, and representatives from other components of the NIH as well as other federal agencies

DISCUSSION:

The discussion began with a plastic surgeon perspective on implants, including descriptions, rupture, and other complications. The estimated number of women with breast implants is 1 million and the estimated percentage done for cosmetic reasons is 75% vs. those for reconstruction, 25%. The surgical strategies and sites used in

breast implants were reviewed; and the three major uses were described, namely cosmetic, correction of congenital deformities, and reconstruction associated with cancer. The major complication is capsular contracture.

The discussion continued with the evaluation of health risks and began with the rheumatologic perspective on case definition issues in diagnosis. There are more than 100 different diagnoses of rheumatic diseases, and arthritis is the most common manifestation, but muscles, skin, and blood vessels are often involved. The classification criteria of arthritis and the connective tissue diseases of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, vasculitis, Sjogren's syndrome, and other miscellaneous diseases were also reviewed. Most diagnoses of rheumatic diseases require subjective and objective evidence of disease that is supported by laboratory or radiographic abnormalities. The bases for American College of Rheumatology classification criteria for rheumatic diseases were discussed, including symptoms (subjective complaints), signs of clinical disease, and laboratory testing. The caveats of laboratory tests were discussed, including the issues of specificity and sensitivity. The process for developing diagnostic criteria includes population studies and tested criteria as well as validation studies. In discussing the extent of reliability among rheumatologists in diagnosing disease, participants described the difficulties in diagnosing fibromyalgia and mixed connective tissue diseases.

Next, clinical perspectives on atypical conditions were presented, including the historical precedent of the Japanese experience, in which women were injected with paraffin plus industrial grade silicone, with reports of classical rheumatic disease, atypical rheumatic disease, and severe local reactions. The participants also discussed the role of silica in silicone breast implants. Some of the immune responses that have been noted in some women with silicone breast implants include antibodies to collagen and antinuclear antibodies. Local diseases associated with silicone breast implants include local features in the breast such as loss of sensation, capsular contraction, implant rupture, and burning pain, as well as other local features such as a rash. In addition, macrophage activation in response to silicone gel implants has been reported, as have increased levels of cytokines in cells obtained from the tissue surrounding silicone breast implants. It was also suggested that certain HLA types (HLA DR53) may be related to predisposition to local or systemic disease. Other manifestations of disease, such as chronic fatigue, skin manifestations, and cognitive dysfunction were also discussed, as well as potential overlap with fibromyalgia.

The participants also provided an epidemiologic perspective on connective tissue diseases and described particular epidemiologic studies that involved silicone breast implants. The first was the study by Gabriel (1994) -- a retrospective cohort study, done in Minnesota, on the risk of connective tissue disease after breast implants. The study included 749 women with implants and about 1500 female controls. The average

followup time was about 8 years. The data did not show an increased incidence of defined connective tissue disease in women with breast implants. There are three potential problems in epidemiologic studies: chance, bias, and confounding factors. The limits of the Gabriel study include the limited ability to detect an increased risk of rare connective tissue disease, and the somewhat short mean followup time. The strengths of this study include the large number of patients, multiple signs and symptoms of connective tissue disease studied, and patient clinical records reviewed.

The second study was that of Sanchez-Guerrero (1995) -- a study of silicone breast implants and the risk of connective tissue disease and symptoms, in the nurses health study cohort (from 1976). In this study, the incidence of connective tissue disease was about what would be expected from other studies. One weakness of this study was that there was not enough power to detect a small increase in the risk of defined connective tissue disease. A strength was that all cases of self-reported rheumatic disease were verified by medical records review.

The aim of a third epidemiologic study was to determine the association between breast implants and classical connective tissue diseases. This was a retrospective cohort study in female health professionals self-reported for breast implants and for connective tissue disease. This study involved a cohort of 395,543 women, of which 10,830 had had breast implants. With the caveats expressed, the results of this study provide evidence against a large hazard of connective tissue disease in women with breast implants, and suggest that there is a small, but statistically significant, 24% increased risk for rheumatic symptoms. The limitations of this study are that the data were self reported on connective tissue diseases (as well as breast implants); the response rate to the baseline questionnaire was only 24%; and there were no details on the types of breast implants nor the reasons for the implants.

The next study discussed was one of early undifferentiated connective tissue disease and was a 10 year, observational study conducted across the country. It included early disease (of less than one year), both defined and undifferentiated, and was conducted in 1982-1987. 410 patients were involved, including those with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and polymyositis/dermatomyositis, as well as undifferentiated connective tissue disease (213 patients). The conclusion of this study was the absence of significant association between prior breast implants and connective tissue diseases. The strengths of this study included the fact that it was an inception cohort, selected for undifferentiated disease, selected prior to the controversy appearing in the press, and it was multicenter. The weaknesses included the potential for under-reporting, the fact that the control group was nonconcurrent, and was population based, and that the study included small numbers of patients.

The immunological response to silicone was described in a mouse model of plasmacytoma in which silicone was injected into the peritoneal cavity. Speakers

emphasized the significant contributions of basic research to understanding the biological responses to silicone. Following that discussion, studies of idiopathic inflammatory myopathies (chronic muscle weakness from muscle inflammation) were described. It was suggested that myositis may develop in some patients with silicone implants. There are some differences in the patients with myositis associated with implants compared to idiopathic myositis including more fibromyalgia, more cognitive dysfunction, and less responsiveness to treatment. The hypothesis that a T cell response may be activated in these patients and the potential relationship with HLA alleles was presented.

Next the FDA perspective was given, including a description of the largest published explant series (by Robinson), in which 63% of the implants had disruptions; 72% of the symptomatic women with implants had disruptions, and 71% of the asymptomatic women with implants had disruptions. This was followed by questions from the public that sought clarification of published epidemiologic studies, asked about the overlap with fibromyalgia and atypical rheumatic disease, and discussed techniques for detection for antibodies.

The afternoon discussion revolved around three questions, (1) Given the current information, is there reason to believe that atypical forms of rheumatic diseases can be defined? (2) Given the current information, is there reason to believe that a possible association may exist between atypical connective tissue disease and silicone breast implants? and (3) Are there other questions that should be addressed on this topic? or What, if any questions should be addressed to this topic?

The discussion was opened by asking if atypical rheumatic disease could be defined. A working definition had been proposed for systemic silicone-related disease (SSRD) including inclusion criteria, exclusion criteria, and minor criteria. Using this definition, symptomatic patients with implants, asymptomatic patients with implants and fibromyalgia patients were screened. Two physicians had to agree on the application of the criteria. 79 out of 100 symptomatic women with silicone exposure met the operational criteria of SSRD. None of the 60 asymptomatic patients with silicone exposure met criteria and 2 of 79 fibromyalgia patients met the criteria of SSRD. In the discussion of defining atypical rheumatic disease, it was noted that patients with idiopathic myositis typically do not have cognitive dysfunction or fatigue or sicca. It was stated that rheumatologists frequently see many patients with atypical rheumatic disease and the potential overlap with fibromyalgia and chronic fatigue syndrome was discussed. There was also discussion of the cultural environment in which there is pressure on physicians to label diseases to satisfy insurance company requirements as well as patient anxiety. It was suggested that it might be possible to develop a working definition for atypical rheumatic disease and then study patients with atypical rheumatic disease and identify the spectrum of signs and symptoms associated, including people with silicone breast implants.

Next, the participants discussed the role of biological markers in aiding in the diagnosis of disease and in the development of epidemiologic studies. The difficulties in using HLA as a biological marker to diagnose disease were noted, while its value in basic research studies was confirmed.

Finally, the challenges in designing an epidemiologic study to show an association between atypical rheumatic disease and silicone breast implants were discussed. For example, it was noted that objective studies cannot be designed if they are based only on subjective diagnostic criteria. In addition, a low association creates a methodology problem. Even with the available diagnostic criteria, there would be concerns about large epidemiologic studies because of false positives. Also, the discussants felt that before the existence of an association between atypical rheumatic disease and silicone breast implants can be substantively addressed, atypical rheumatic disease needs to be defined.

In conclusion, the participants acknowledged the need for the development of diagnostic criteria for atypical rheumatic disease and for additional basic research on the components of silicone as well as biological responses to silicone.

OUTCOMES:

- The NIAMS has approached the American College of Rheumatology to explore the possibility of the ACR defining atypical rheumatic disease.

- The NIAMS hopes to promote basic research on host responses to materials used in medical implants and the Institute is participating in an NIH Request for Applications on Tissue Engineering, Biomimetics, and Medical Implant Science.

ATYPICAL RHEUMATIC DISEASES AND SILICONE BREAST IMPLANTS WORKSHOP

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HIGHLIGHTS OF THE RECENT IMMUNOLOGY OF SILICONE WORKSHOP, NATIONAL CANCER INSTITUTE (MARCH 13-14, 1995)

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This workshop started with the chemistry of silicon, silicon dioxide and how material from nature (silicon) is used for manufacturing silicone gels(1) and continued with different presentations to cover the following issues:

A. Silicone Migration to Distant Tissues.

By nuclear magnetic resonance (NMR) and histopathology, it was shown that silicone migrates from implant site to adjacent tissues and distant organs, such as the liver and spleen (2-5). It was also shown that silicone is not an inert material but undergoes chemical transformation in a biological environment. Using NMR spectroscopy and ^{29}Si, animal tissues exposed to silicone and blood samples from women with gel-filled breast implants showed the presence of silicone, partially hydrolized silicone, silica and other silicon compounds. This Si spectroscopy was completely negative for silica, silicon and silicon dioxide in the blood of non-implanted patients. The reaction of monomer to polymer can therefore go both ways and as a result of the aging of material, polymer is broken down to monomer.

$$\text{MONOMER} \;\underset{\longrightarrow}{\longleftarrow}\; \text{POLYMER}$$

Therefore, if this polymer is placed into the body, after a few years break down products of the polymer are detected in the blood and tissues (2-7).

B. Binding or Adsorption of Proteins to Silicone.

Polydimethylsiloxane, similar to other hydrophobic polymers (polystyrene, polypropylene, nitrocellulose), adsorbs soluble proteins with high avidity under physiological conditions (8). Using atomic force microscopy, it was revealed that the potential adsorptive surface of polydimethylsiloxane is much greater than polystyrene used in the manufacturing of Elisa plates. Therefore, the data presented raised a philosophical issue as to why hydrophobic substances are used for medical prostheses in an environment in which cell surfaces and soluble proteins are typically negatively charged and repel adherence. Adherence or binding of polydimethylsiloxane or other silicone byproducts to body proteins changes the self material to non-self and immunological reaction to this complex therefore occurs, especially in an individual having predisposition or genetic makeup to autoimmune diseases (9-12). Moreover, by using macrophage-like cells and fibroblast cell lines, it was shown that inclusion complexes of α-cyclodextrin and silicone compounds have a cytotoxic effect as well as DNA-membrane damaging properties. So in addition to the autoimmune properties of silicone complexes, the lethal effect on cells also was shown (13).

C. **Genetic Predisposition to Silicone-Induced Immunologic Disorder.**

HLA typing was performed in order to examine an association between the symptoms seen in implant patients and the HLA antigen. Data from this study did suggest that symptomatic patients with implants share important genetic characteristics (primarily HLA-DR53 positivity) which differentiates them from their asymptomatic counterparts. Therefore DR53 may be a marker for women who are predisposed by their HLA genotype to develop an immune-mediated reaction following exposure to some component of silicone gel breast implants (12).

This genetic predisposition issue was further confirmed by the study of T-cell proliferation using silicone in different strains of mice. It was demonstrated that injected silicone gel induces an in vitro T-cell proliferative response in certain strains of mice (BALB/C,C57) but not in DBA. This response is mediated by silicone-induced peritonial cells which stimulate spleen, lymph and mesenteric lymph node cells from syngeneic mice injected subcutaneously with silicone gel but not with saline (14).

Environmental factors such as housing and the amount of fat in the diet affected the degree of T-cell proliferative response due to silicone injection. With a low fat diet, a much lower T-cell response was obtained (14).

D. **Silicone Gel Acts Like an Adjuvant.**

One of the properties of adjuvants is the enhancement of immunologic responses to conventional antigens. Comparing silicone gel to classical adjuvants again showed that silicone gel has the capacity of enhancing immunological responses to different antigens. Furthermore, it was demonstrated that collagen-induced arthritis in dark agouti (DA) rat was much higher than the control saline-injected group. It was concluded that silicone gel taken from a commercial breast implant is capable of mediating collagen-induced arthritis in susceptible strains of rat (15). It may be concluded therefore that different autoreactive antibodies detected in the sera of patients with silicone breast implants are the result of adjuvant characteristics of silicone gel implants which have been reported by different investigators. These include ANA, thyroid antibodies, phospholipid antibodies, other tissue antibodies, myelin basic protein antibodies, myelin associated glycoprotein, ganglioside and sulfatide antibodies with low levels of C3 and C4 complement(10,11,16-18). Immune complexes and immunoglobulin levels were also reported to be elevated in 23% of the patients, especially when serum electrophoresis and immunofixation for kappa and lambda chains were performed (19). This elevation of immunoglobulin levels led to the possible development of plasmacytoma and multiple myeloma due to silicone gel implants. In genetically susceptible mice (BALB/C), it was shown that silicone gel, but not silicone oil, induced plasmacytoma , a cancer of the plasma cell (20).

And finally, based on the reports and presentations of several investigators to the National Cancer Institute, 18 cases of multiple myeloma (especially of Immunoglobulin-G) have been detected so far in patients with silicone breast implants.This excessive number of multiple myeloma among patients with silicone breast implants certainly warrants further investigation and may justify the inclusion of immunoglobulin levels and kappa-lambda monoclonal measurement as part of the silicone implant patient's yearly check-up.

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In summary, as we had hypothesized in earlier publications (29,30), silicone, after it is released from the bag, will reach distant tissues and organs where body proteins absorb or adhere. This complex of silicone with human body proteins will then initiate host reactivity against silicone and macromolecules within the microenvironment of the implant. As a result, autoreactive antibodies are produced which may in turn cause atypical connective tissue disease, atypical neurological disorder, immunologic disorders and possible cancer (at least multiple myeloma).

Based on the results presented in this workshop and upon earlier studies, patients who present with complaints of silicone-induced immune dysfunction syndrome (SIIDS) deserve objective evaluation. However, because of the multi organ effects of silicone and the presence of different laboratory abnormalities in different patients, there is no single test that may help in the diagnosis of this complex disease. Therefore, quantitative evaluation of both cellular and humoral immunity with the major emphasis on non-specific tissue antibodies by western blot assay, myelin associated glycoprotein antibodies (MAG), ganglioside, sulfatide and silicone surface associated antibodies are all needed to diagnose atypical connective tissue disease or atypical neurological disorder, the most common disorders among these patients(20-30). Because of the described incidences of multiple myeloma in patients with silicone implants, measurement of immunoglobulin levels by immunofixation test for the kappa and lambda chains of IgG, IgM, and IgA and HLA typing should be added to the long list of laboratory testing.

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Detection of Monoclonal Gammopathy of Undetermined Significance (MGUS), Multiple Myeloma, Waldenstrom's Macroglobulinemia, Amyloidosis and Lymphoma by Immunofixation Test in Patients with Silicone Implants.

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Since the recent workshop about the immunology of silicone by the National Cancer Institute and report of excessive number of multiple myeloma cases among patients with silicone breast implant, many questions have been raised by the support group leaders and the patients.

This summary is written in order to address some of these questions.

Immunoglobulin Quantitation In Serum, Urine, And Spinal Fluid.

Diagnosis and monitoring of clinical course of many diseases is possible by measuring the concentration of monoclonal immunoglobulin or paraprotein. The spectrum of abnormalities in serum immunoglobulin concentrations is broad. Abnormal concentrations range from a virtual absence of one or more of the three major classes (immunoglobulin G [IgG], IgA, and IgM) to polyclonal increases in one or more immunoglobulins. IgA deficiency is the most common selective immunoglobulin defect. Polyclonal increases in immunoglobulins are commonly seen in chronic inflammation; for example, IgA is increased in association with chronic liver disease. In most cases, quantitation of immunoglobulins is performed because the patient is clinically suspected to have an immunoglobulin deficiency or a monoclonal immunoglobulin.

Patients with monoclonal immunoglobulins include those with multiple myeloma, but monoclonal immunoglobulins also occur in other B-cell malignancies such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia and in benign monoclonal gammopathy.

CLASSIFICATION AND DIAGNOSIS OF MONOCLONAL GAMMOPATHIES BY IMMUNOFIXATION

The monoclonal gammopathies are a group of disorders characterized by the proliferation of a single clone of plasma cells that produce a homogeneous monoclonal (M) protein. Each monoclonal protein consists of two heavy polypeptide chains of the same class and subclass and two light polypeptide chains of the same type. In contrast, an increase in polyclonal immunoglobulins consists of one or more heavy-chain classes and both light-chain types.

The different types of monoclonal immunoglobulins are designed by capital letters that correspond to the class of their heavy chains, which are designated by Greek letters, γ in immunoglobulin G(IgG), α in IgA, μ in IgM, δ in IgD, and ϵ in IgE.

The normal assortment of immunoglobulin molecules comprises minute amounts of homogeneous proteins from many diverse single clones of plasma cells and so is polyclonal. If due to exposure to chemicals, including silicone or mutation, a single clone escapes the normal controls over its multiplication, it reproduces excessively and synthesizes an excess of protein with a single heavy-chain class and subclass and light-chain type. This monoclonal protein often is associated with a neoplastic process (Fig. 1).

The monoclonal gammopathies may be classified as follows:

I. Malignant monoclonal gammopathies.
   - A. Multiple myeloma (IgG, IgA, IgD, IgE and free light chains)
     1. Overt multiple myeloma
     2. Smoldering multiple myeloma
     3. Plasma cell leukemia
     4. Nonsecretory myeloma
   - B. Plasmacytoma
     1. Solitary plasmacytoma of bone
     2. Extramedullary plasmacytoma, solitary and multiple
   - C. Malignant lymphoproliferative diseases
     1. Waldenstrom's macroglobulinemia or primary macroglobulinemia (IgM)
     2. Malignant lymphoma
   - D. Heavy-chain diseases (HCD)
     1. γ HCD
     2. α HCD
     3. μ HCD
     4. δ HCD
   - E. Amyloidosis
     1. Primary
     2. With myeloma

     (Secondary, localized and familial amyloidoses have no monoclonal protein)

Differentiation Of MGUS From Multiple Myeloma And Macroglobulinemia

The term monoclonal gammopathy of undetermined significance (MGUS) denotes the presence of a monoclonal protein in persons without evidence of multiple myeloma, macroglobulinemia, amyloidosis, or other related disease. The term benign monoclonal gammopathy is misleading because it is not known at the time of diagnosis whether a monoclonal protein will remain stable and benign or will develop into symptomatic, multiple myeloma, macroglobulinemia or amyloidosis.

Persons with MGUS usually have (i) less than 3.0 g of the monoclonal protein per dl in the serum and none or small amounts of Bence Jones proteinuria, (ii) fewer than 5% plasma cells in the bone marrow aspirate, and (iii) no anemia, hypercalcemia, renal insufficiency, or osteolytic lesions (unless caused by other disease). The only basis for deciding that the condition is benign is the absence of an increase of the monoclonal protein and absence of immunoproliferative disease during long-term follow-up. Differentiation of MGUS from myeloma or macroglobulinemia is fraught with difficulty at the time of recognition of the monoclonal protein. Help may be derived from the size of the serum monoclonal protein, levels of normal polyclonal or background immunoglobulin, presence and amount of Bence Jones proteinuria, number of plasma cells int he bone marrow, presence of osteolytic lesions, plasma cell-labeling index, serum β_2-microglobulin level, presence of J chains in plasma cells, and presence of monoclonal idiotypic peripheral blood lymphocytes.

The serum level of the monoclonal protein is often helpful. A monoclonal protein level of 3 g/dl or more usually indicates overt multiple myeloma or macroglobulinemia, but some exceptions, such as smoldering myeloma, do exist.

The association of Bence Jones proteinuria with a serum monoclonal protein usually indicates a neoplastic process. However, additional tests are necessary in order to confirm neoplasm.

The presence of more than 5% plasma cells in the bone marrow is suggestive of myeloma; but in some patients who have a more pronounced plasmacytosis, the process has remained stable for long periods. Conversely, single bone marrow specimens from patients with overt myeloma may have fewer than 5% plasma cells because the distribution of malignant cells may be spotty. Although plasma cells show morphologic atypia in multiple myeloma, these features also may appear with MGUS and smoldering multiple myeloma.

The most reliable means of distinguishing a benign course from a malignant course is the serial measurement of the monoclonal protein. If the serum monoclonal protein is less than 2.0 g/dl, electrophoresis should be repeated 6 months after its discovery; if the concentration has not increased, electrophoresis should be repeated annually thereafter. If the monoclonal protein is 2.0 g/dl or more and there is no evidence of myeloma or macroglobulinemia after appropriate laboratory tests, electrophoresis should be repeated 3

months after the recognition of the monoclonal protein. If electrophoresis shows stability, it should be repeated in 6 months, and if there is still no progression, electrophoresis should be performed every 6 to 12 months, thereafter depending on the clinical findings. If the monoclonal protein increases more than 0.5 g/dl, immunoelectrophoresis of a 24-h urine specimen and a hemoglobin determination should be done. Determination of serum calcium and creatinine levels, as well as bone marrow and roentgenographic examinations, should be considered. If a monoclonal protein is present in the urine, the patient should be followed up more closely by the Immunofixation Test. And finally, the clinician must continue the periodic reexamination of patients with MGUS to determine whether the disorder is benign or is the initial manifestation of multiple myeloma, systemic amyloidosis, macroglobulinemia, or other malignant lymphoproliferative disorders. Finally, patients with silicone implants should be examined annually by immunofixation tests for possible detection of monoclonal immunoglobulins.

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IMMUNOFIXATION TEST FOR DETECTION OF:

1) Monoclonal Gammopathy of Undetermined Significance (MGUS)

2) Multiple Myeloma

3) Waldenstrom's Macroglobulinemia

4) Amyloidosis

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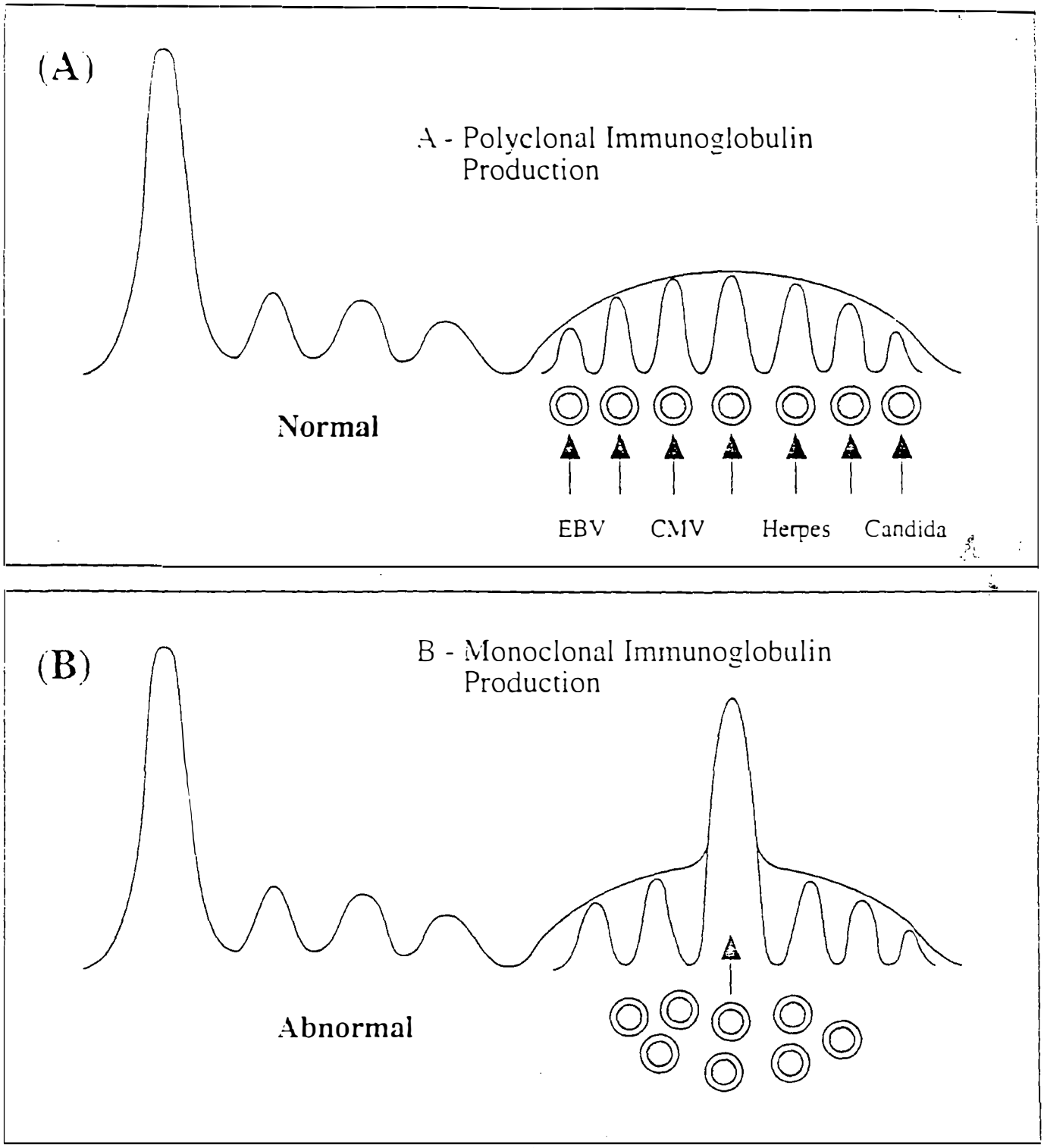

FIG. 1 Polyclonal and Monoclonal plasma cell proliferation and immunoglobulin production.

(A) Broad outline comprising small peaks of many different homogeneous proteins that have been produced by many different plasma cell clones (Polyclonal) is seen in the blood of normal individuals. For example one plasma cell for EBV and the others for CMV, Herpes or Candida. Each immunoglobulin is presented in normal amount.

(B) A narrow and tall peak of homogenous protein produced by a clone of cells (which are originated from a single cell) is observed in blood or urine of patients with Monoclonal Gammopathy of Undermined Significance (MGUS), multiple myeloma, macroglobulinemia, amyloidosis or other related diseases.

II. Monoclonal gammopathies of undetermined significance (MGUS)
   A. Benign (IgG, IgA, IgD, IgM and, rarely, free light chains)
   B. Associated with neoplasms of cell types not known to produce monoclonal proteins
   C. Biclonal gammopathies.

Laboratory Methods For The Study Of Monoclonal Proteins

Analysis of the serum or urine for monoclonal proteins requires a sensitive, rapid, and dependable screening method to detect a monoclonal protein and a specific assay to identify it according to its heavy-chain class and light-chain type. For this, immunofixation should be employed to confirm the presence of a monoclonal protein and to distinguish the immunoglobulin class and light-chain type of which it is made.

Analysis of serum for monoclonal proteins

Serum protein immunofixation should be done in all cases in which multiple myeloma, macroglobulinemia, or amyloidosis is suspected. In addition, the test is indicated in any case of *unexplained weakness or fatigue*, *anemia*, *elevation of the erythrocyte sedimentation rate*, *back* pain, osteoporosis, or *osteolytic lesions or fracture*, immunoglobulin deficiency, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections Serum protein immunofixation also should be performed in peripheral neuropathy, carpal tunnel syndrome, refractory congestive heart failure, nephrotic syndrome, orthostatic hypotension, or malabsorption, because a localized band or spike is strongly suggestive of primary amyloidosis.

After immunofixation, formation of a discrete band is most suggestive of monoclonal gammopathy of undetermined significance, multiple myeloma, or Waldenstrom's macroglobulinemia, but monoclonal peaks may also occur in amyloidosis and in lymphoma.

During immunofixation, the appropriately diluted serum or concentrated urine sample is placed in a small trough in 1% agarose. Electrophoresis is performed and immediately afterward, monospecific antisera are placed over the electrophoresed protein. Excess protein is removed by washing in saline, and bands corresponding to an antigen-antibody complex remain. This is stained and read for the formation of abnormal bands.

A sharp, well-defined band of a single heavy-chain class and light-chain type is seen in monoclonal gammopathy, while broad, diffuse, heavily stained bands with heavy- and light-chain antisera are characteristic of a polyclonal gammopathy.

Immunofixation may be helpful in detecting monoclonal Bence Jones proteins. Various concentrations of urine (urine should be concentrated 100 to 200 times) are electrophoresed on agarose gel, and the gel is overlaid with monospecific antisera. Formation of a localized band indicates the presence of a monoclonal protein. By application of immunofixation technique to cerebral spinal fluid and detection of oligoclonal band, it is possible to diagnose multiple sclerosis or atypical neurologic disorder seen in patients with silicone implants.