

ASIA: a new disease induced by adjuvants

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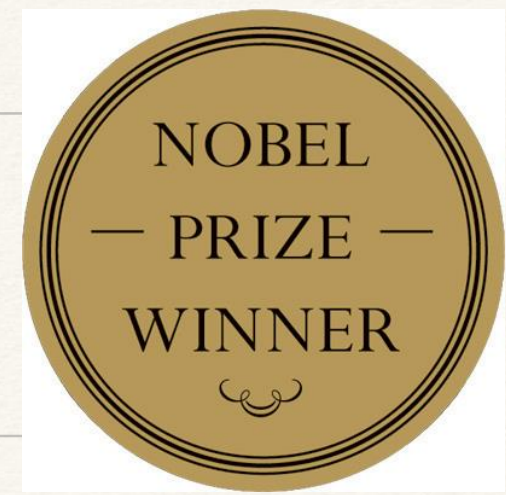


Faculty Disclosure

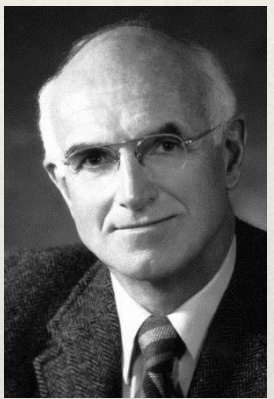
Company	Nature of Affiliation
# InflaRx	• Chairman DSB (Phase II trials anti-inflammatory drugs)
• Company ABC, Company XYZ	

Off-Label Product Usage
None

Organ Transplantation

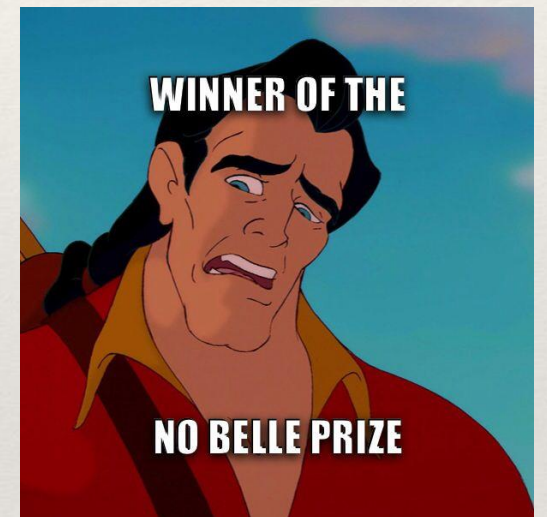


- ❖ Since 1904 many attempts; failed due to rejection
- ❖ 1954: Murray successful kidney Tx (kidney from identical twin)
- ❖ 1961: use of azathioprine to suppress rejection
- ❖ 1978 introduction ciclosporin; increase of 1 yrs survival of kidney Tx from 60% to 90%
- ❖ Bone marrow, Lung, Liver, Heart Tx etc.



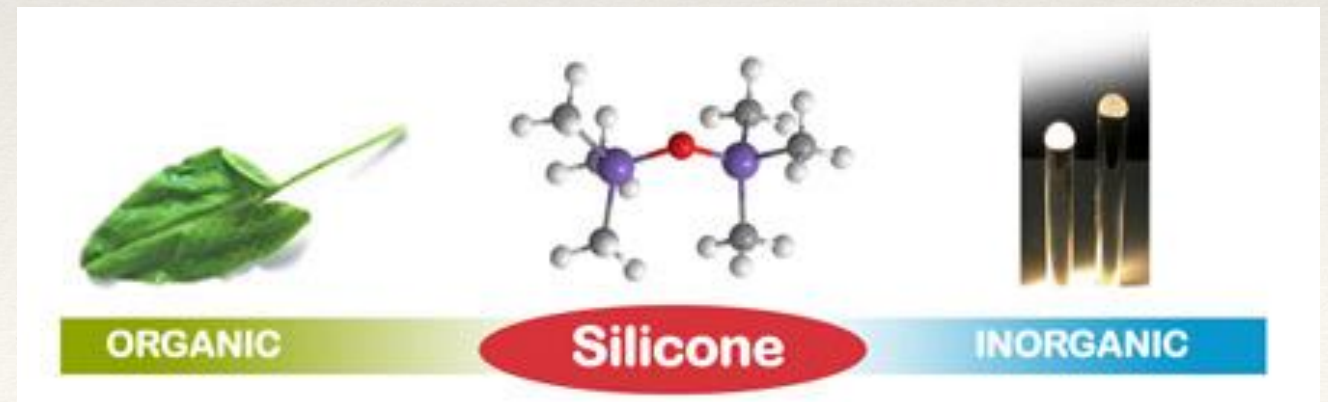
Medical device implantation

- ❖ Since 1898 paraffin, ivory, glass, steel balls, ground rubber, animal cartilage, foam sponges, silicone injections tried: no cosmetic success; caused breast illness
- ❖ 1962 Cronin and Gerow: silicone breast implants
 -*silicones are inert*
- ❖ 1964 saline breast implants
- ❖ 1967 implants not inert
- ❖ 1982 patients may develop autoimmune diseases



History silicone breast implants

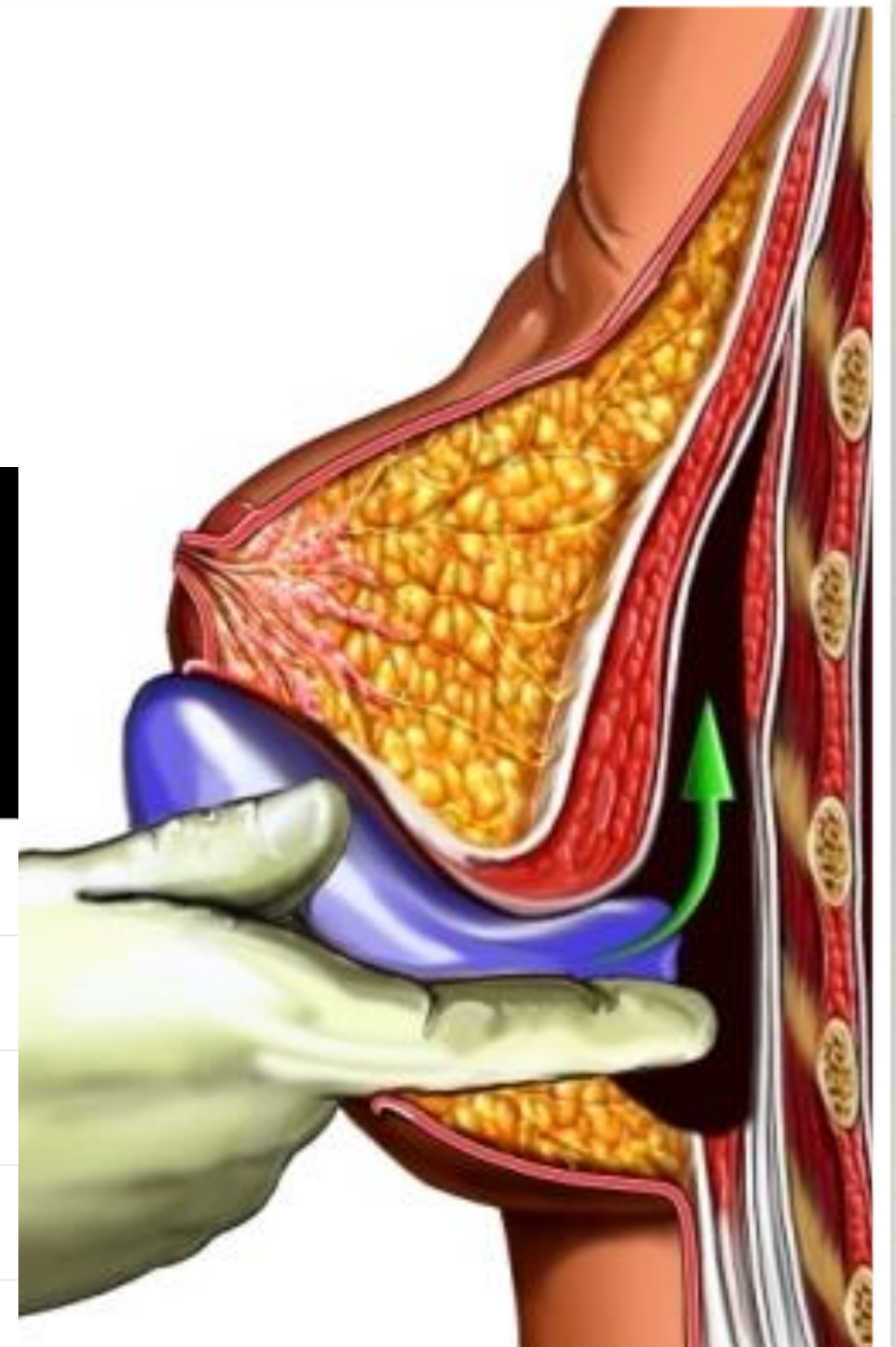
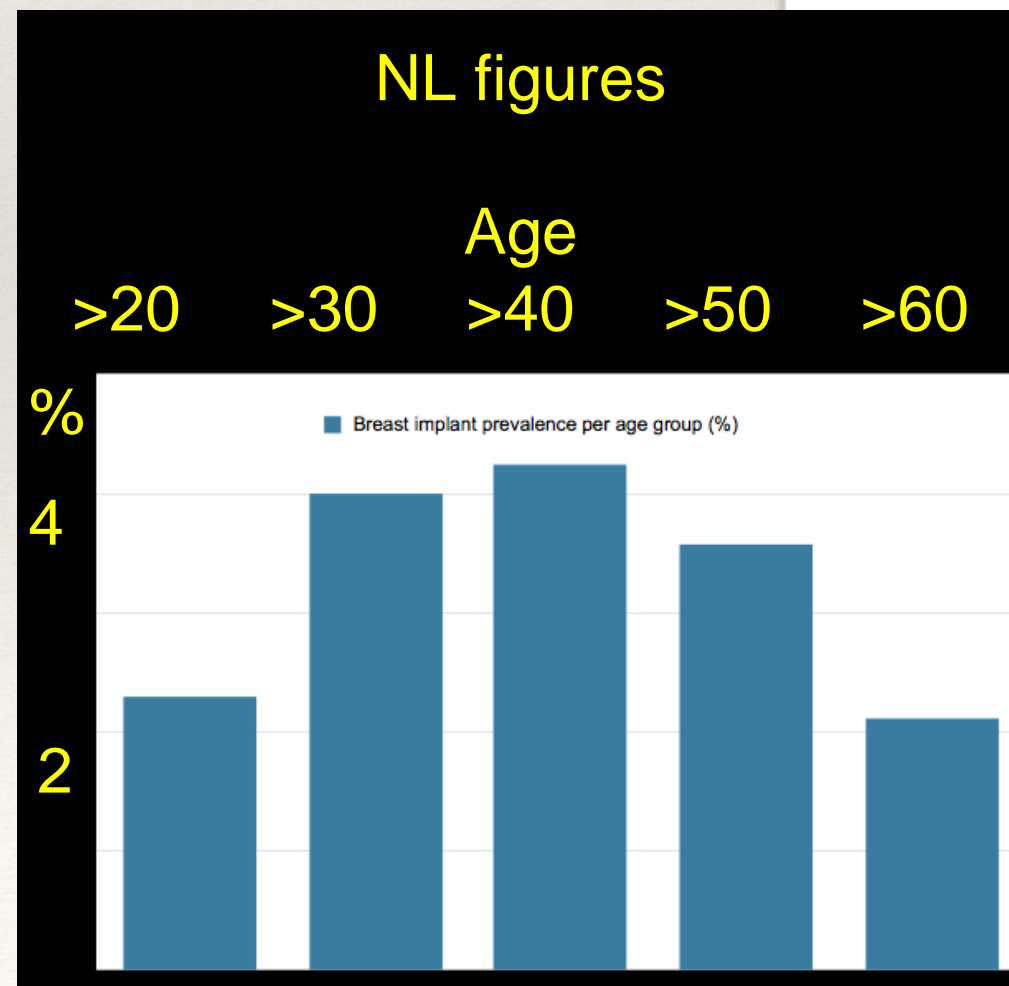
- ❖ 1962: first silicone breast implants (SBI) Cronin-Gerow Implant
- ❖ 1963-1964: first case-reports silicone related complaints and auto-immune diseases
- ❖ 1992 - 2006: FDA's voluntary moratorium
- ❖ 2009 - 2010: PIP affaire
- ❖ 2011: FDA safety warning on ALCL
- ❖ 2015: Silimed affaire
- ❖ 2019: France ban on textured Allergan implants



Silicone Breast Implants (SBI)

- ❖ 2-4 % of women have SBI (USA and the Netherlands)
70% cosmetic
30% reconstructive

- ❖ Worldwide:
10 million
SBI

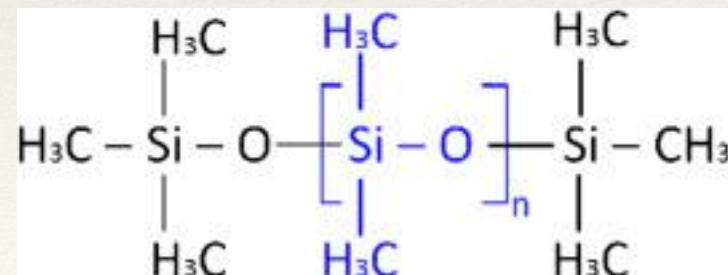


What does WIKIPEDIA say:

Polydimethylsiloxane (PDMS) belongs to a group of polymeric organosilicon compounds that are commonly referred to as silicones.

PDMS is the most widely used silicon-based organic polymer, and is particularly known for its unusual rheological (or flow) properties.

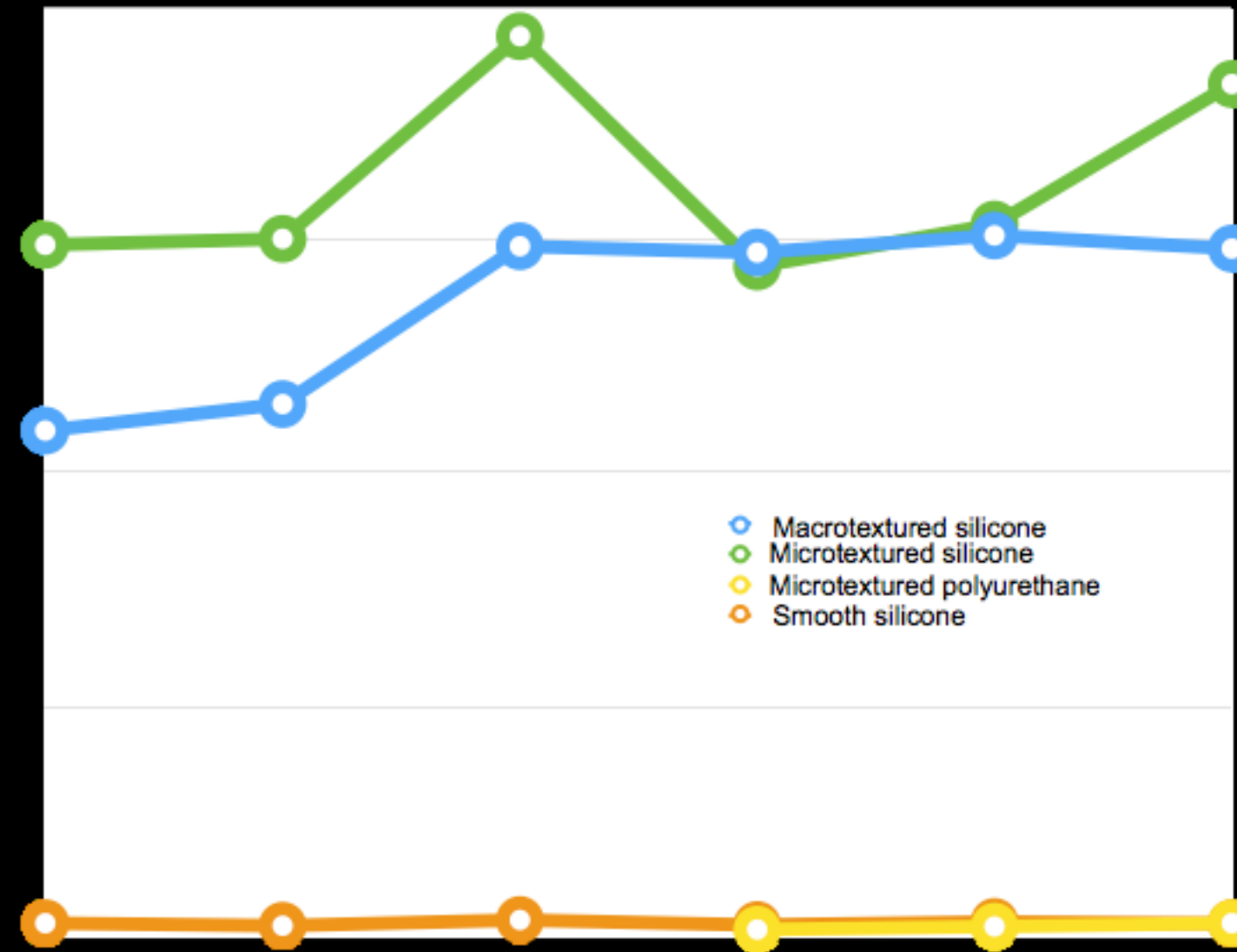
PDMS is optically clear, and, in general, inert, and non-toxic



Capsular formation after breast augmentation

- ❖ Occurs in > 50 % of women
(Caldiero et al. 2018)
- ❖ More often after implantation of "smooth" implants; less often after implantation of "textured" implants

Smooth implants nearly never used in the Netherlands

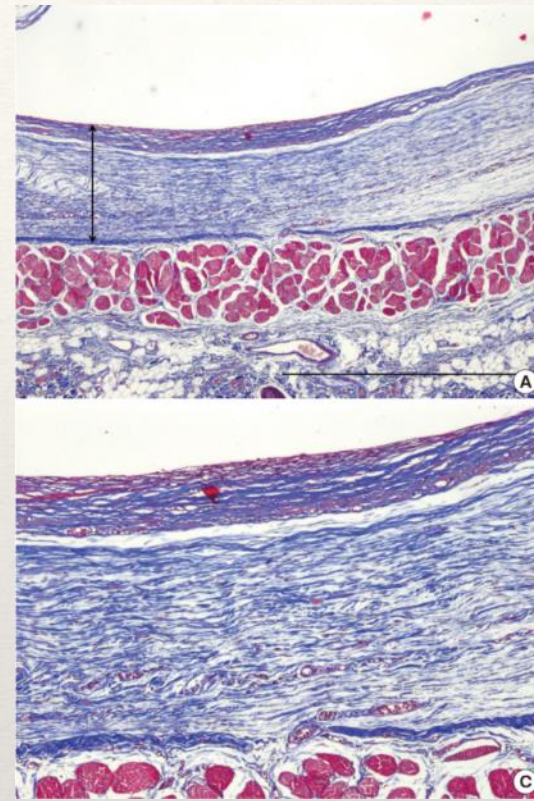


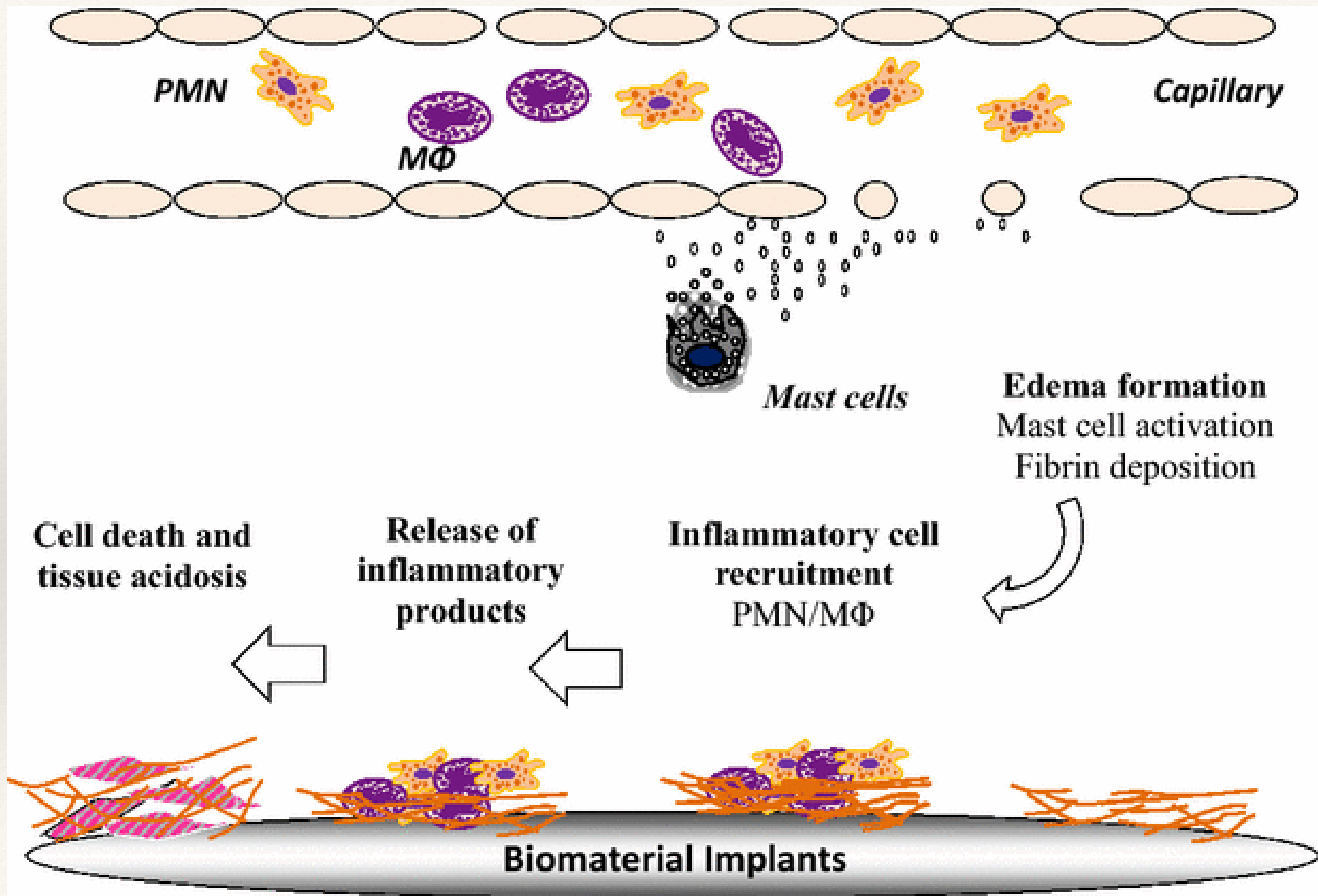
In both animals and humans silicone breast implants are NOT inert *IN VIVO*

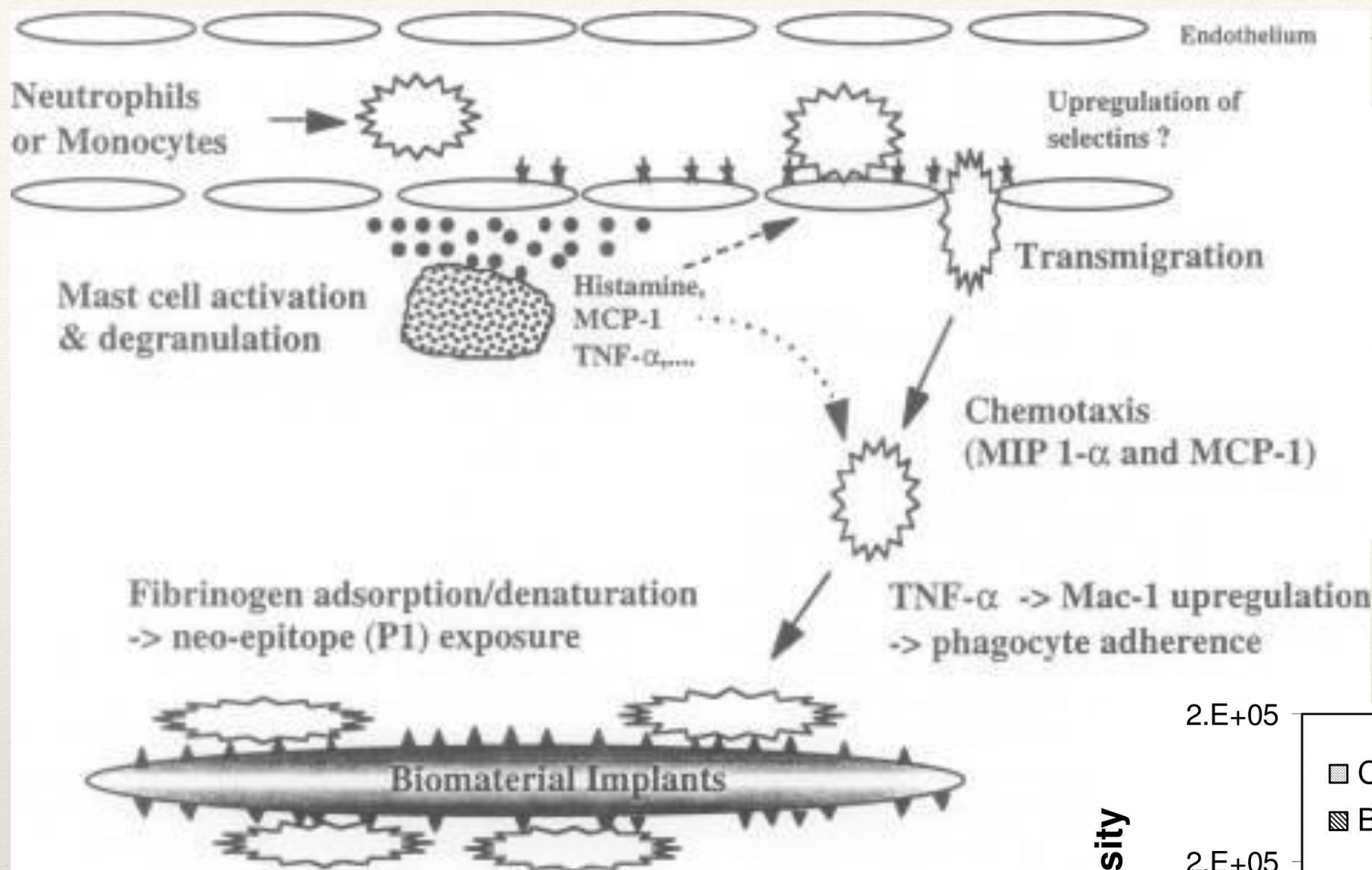
In vitro stimulation with silicones:
no T cell activation

Ex vivo analysis of the capsule:
activated T cells

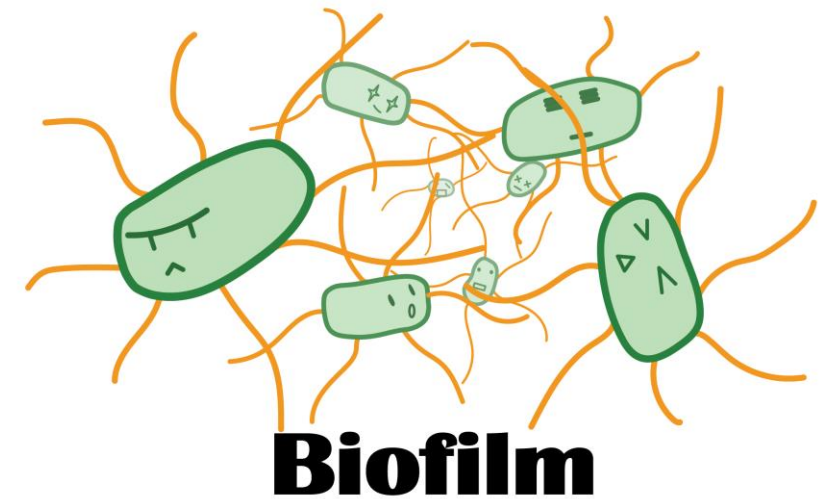
FACS analysis of the T cells from the capsule:
predominance of Th1/Th17 cells and failing Tregs





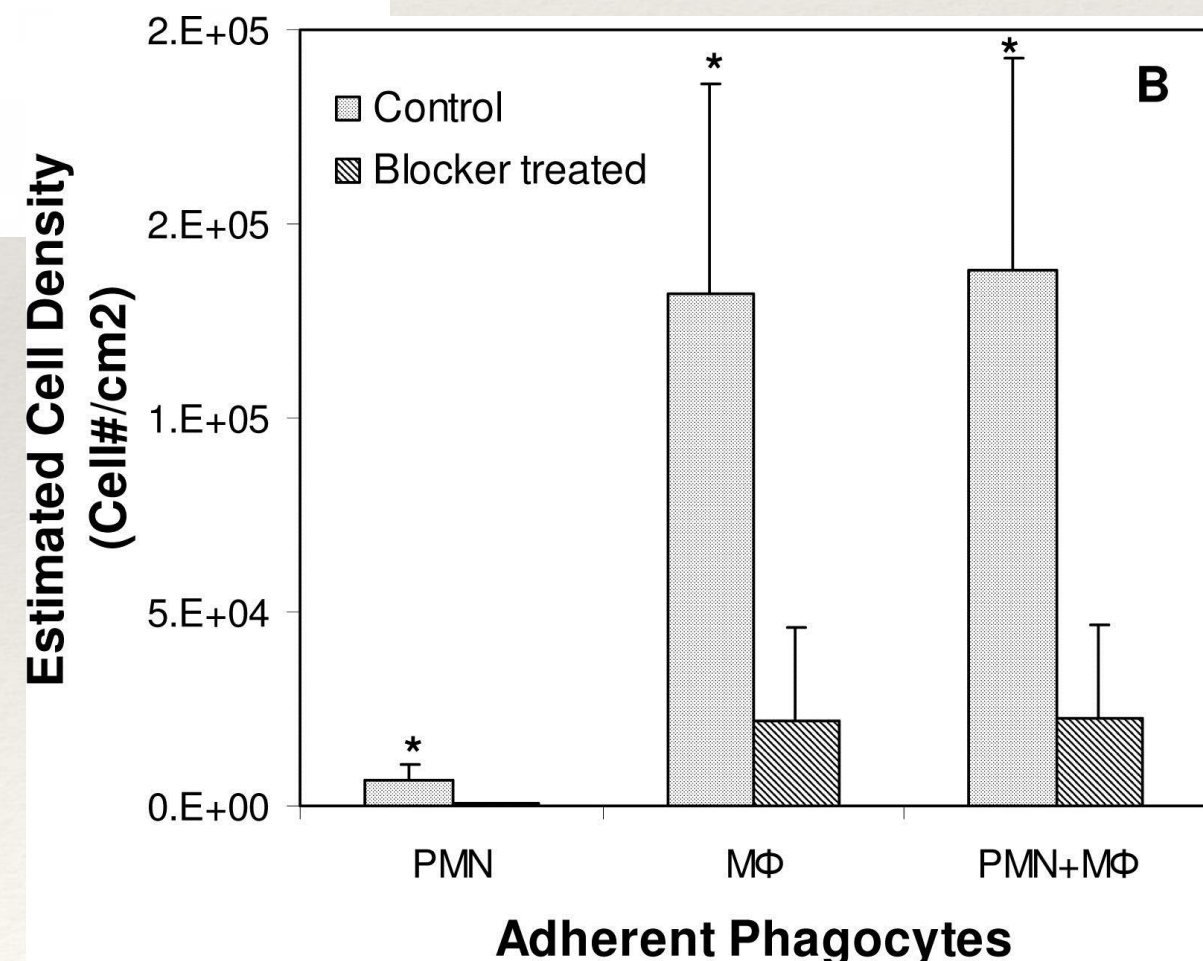


Another factor:
Biofilm



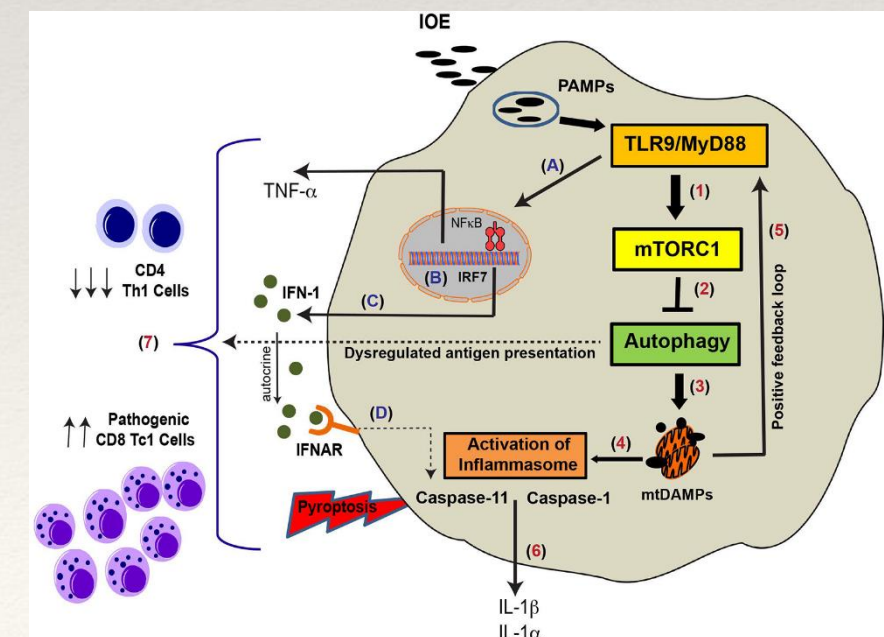
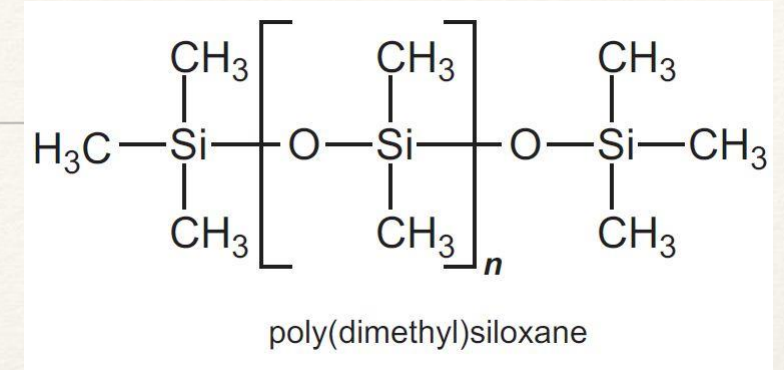
Immediately after implantation proteins and phagocytes are attracted; this process is histamine mediated

Studies by Tang et al.



Implantation of SBI is associated with activation of the immune system

- ❖ Patients develop local complications (capsule formation)
- ❖ Patients develop symptoms such as flu-like disease, fatigue, myalgias ("breast implant illness" "human adjuvant disease" "ASIA")
- ❖ The immune system is not able to recover from the chronic stimulation: immune deficiency resulting in frequent infections
- ❖ The immune system makes "mistakes": auto-immune diseases, allergy and monoclonal proliferation (non-Hodgkin lymphoma such as ALCL)

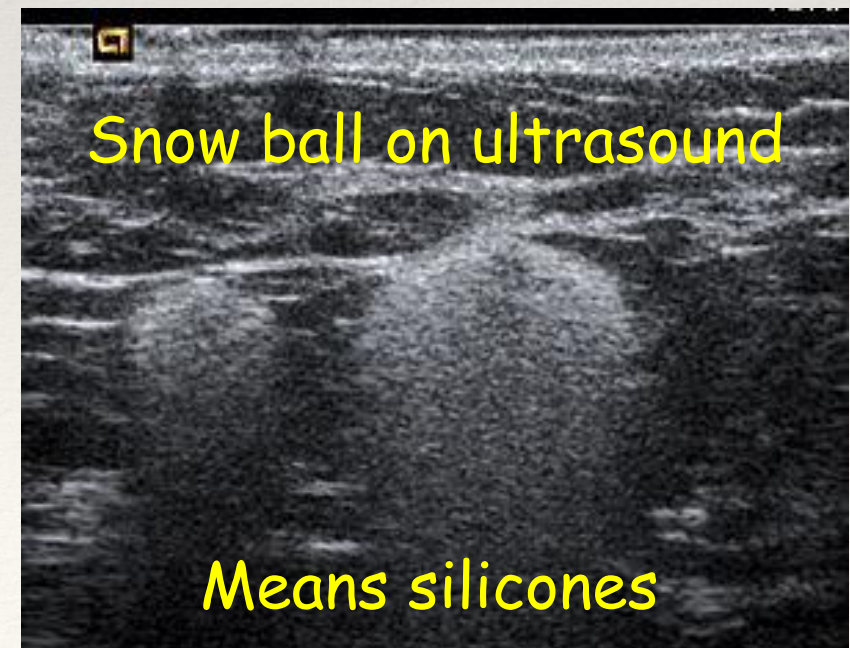
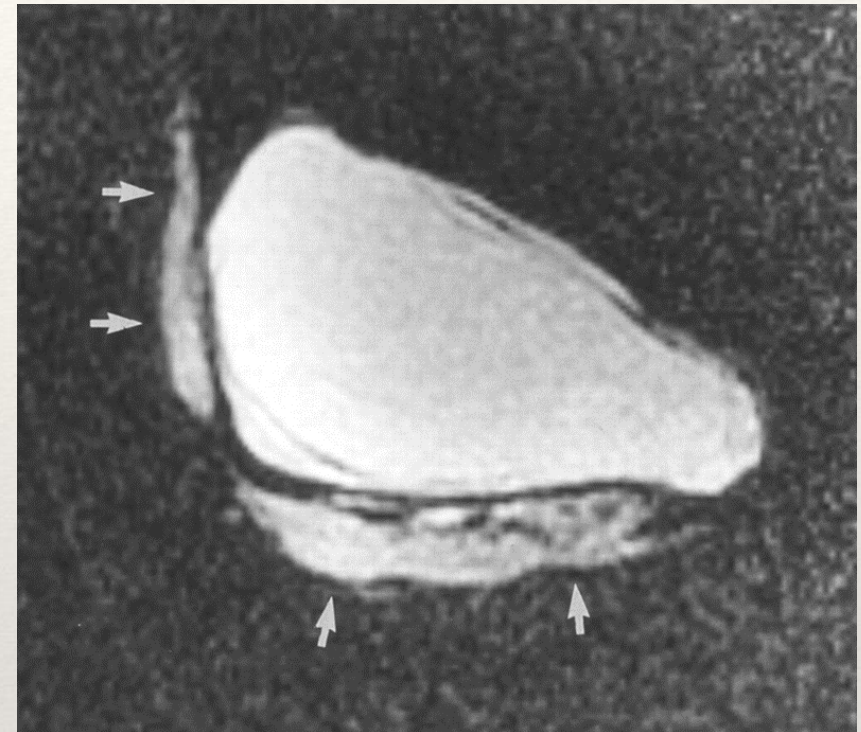


Is it possible that local implantation in the breast causes systemic effects ?

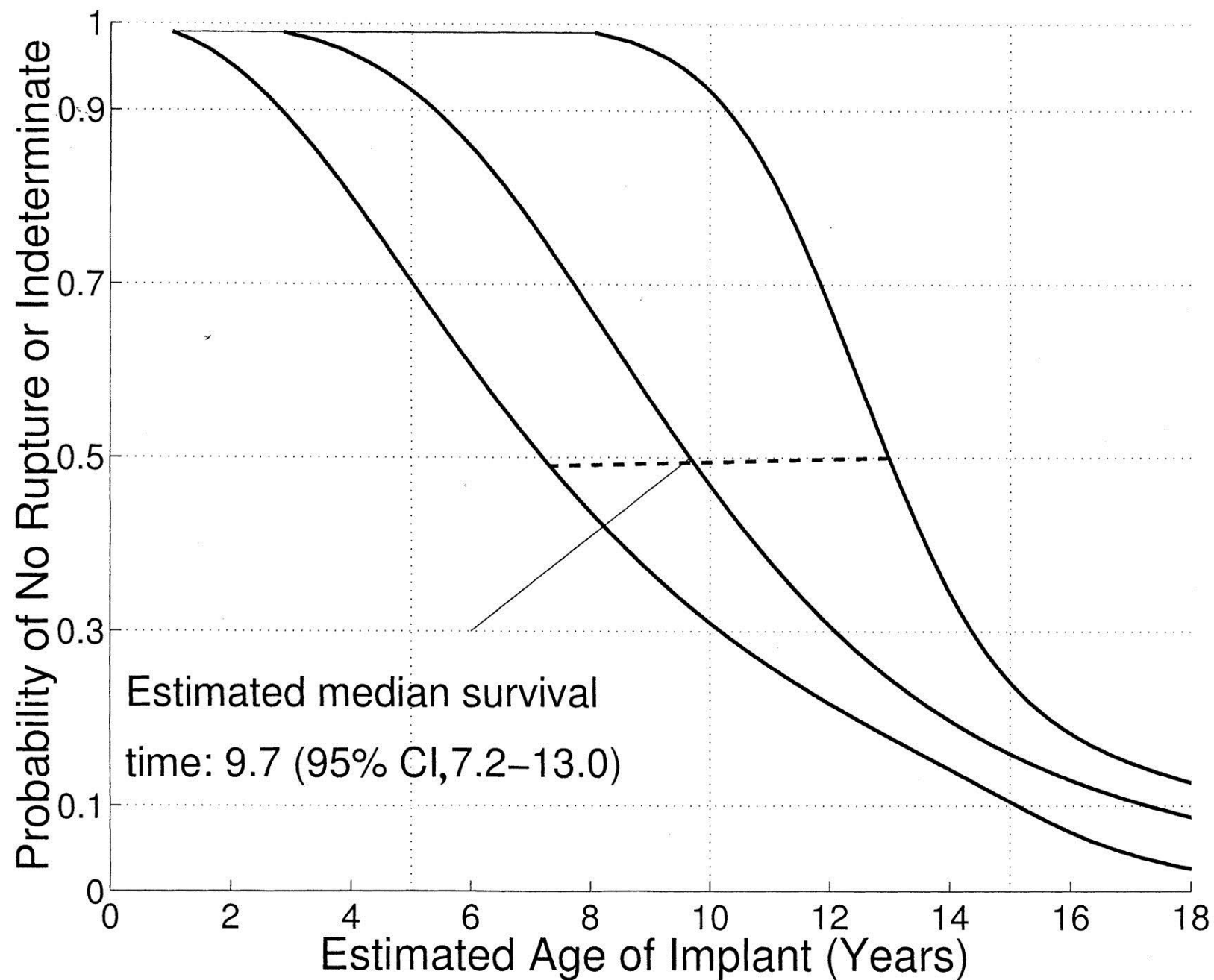
- ❖ SBI may rupture
More often complaints
after SBI rupture

Brown SL et al. J Rheumatol 2001

- ❖ SBI may bleed



Estimated implant ages for probabilities of ruptured or indeterminate implants.



Newer SBI implants

Allergan 2 yrs: 0.5%

Mentor 3 years: 1%

Corroneos et al 2019

Older SBI implants



Brown S L et al. AJR 2000;175:1057-1064

Figures for gel bleed are not available

Autoinflammatory/autoimmunity syndrome induced by adjuvants (Shoenfeld's syndrome) : a new disease

Major Criteria:

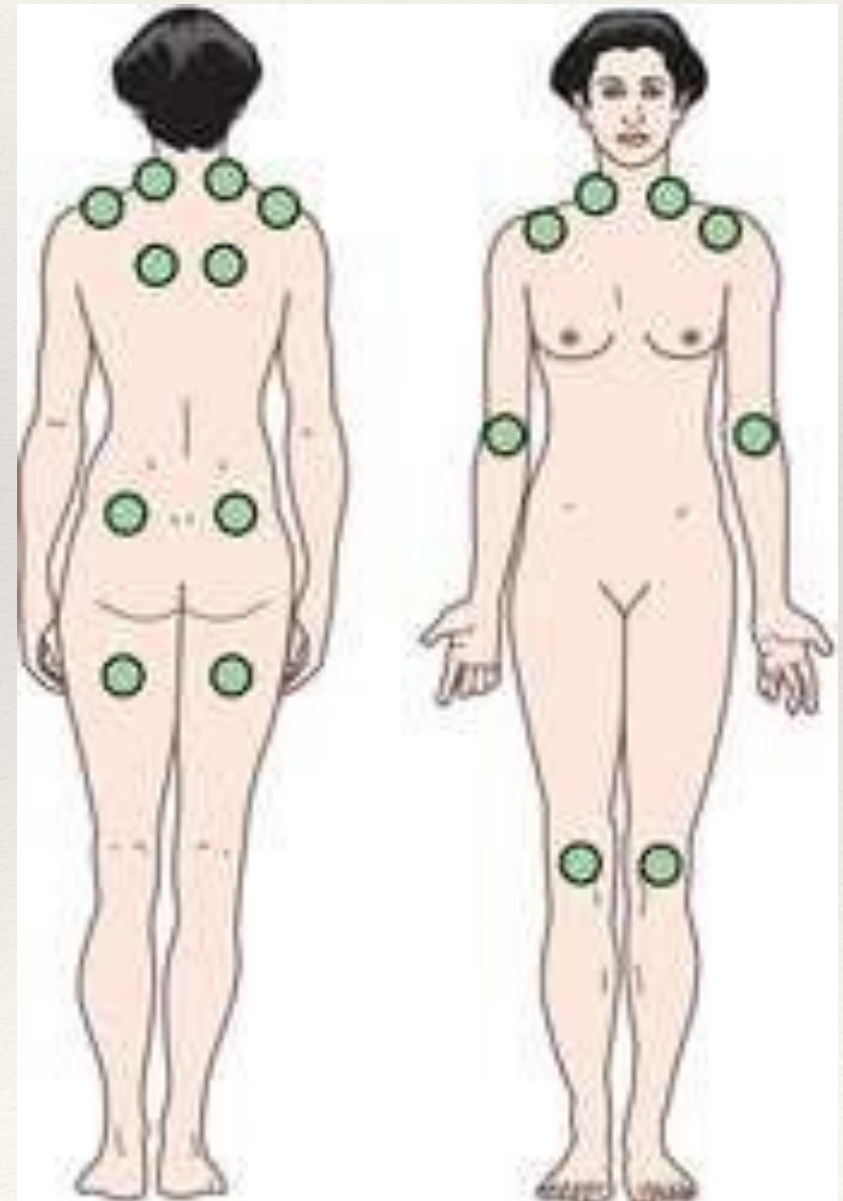
- Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
- The appearance of 'typical' clinical manifestations:
 - Myalgia, Myositis or muscle weakness
 - Arthralgia and/or arthritis
 - Chronic fatigue, un-refreshing sleep or sleep disturbances
 - Neurological manifestations (especially associated with demyelination)
 - Cognitive impairment, memory loss
 - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria:

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syn.)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (i.e. MS, SSc)

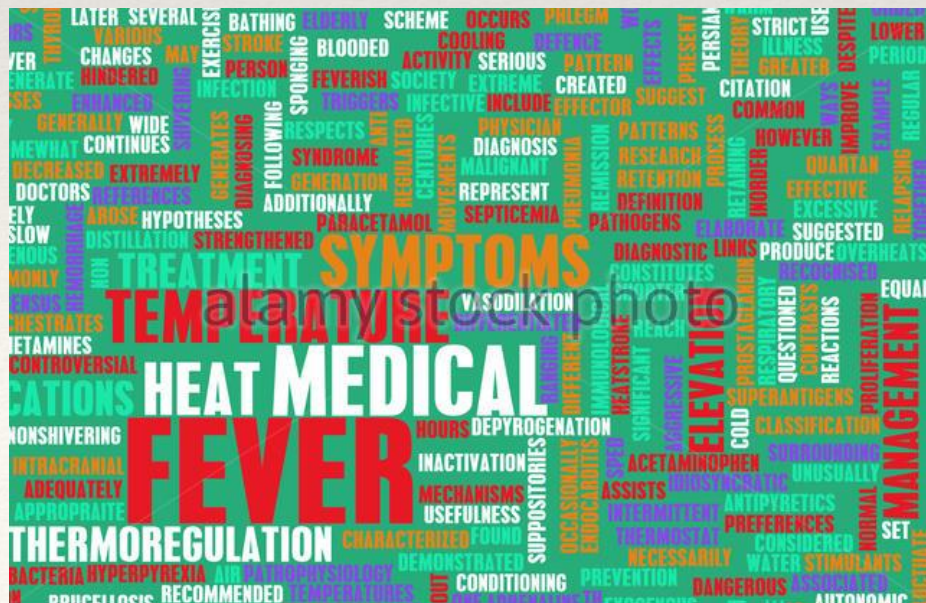
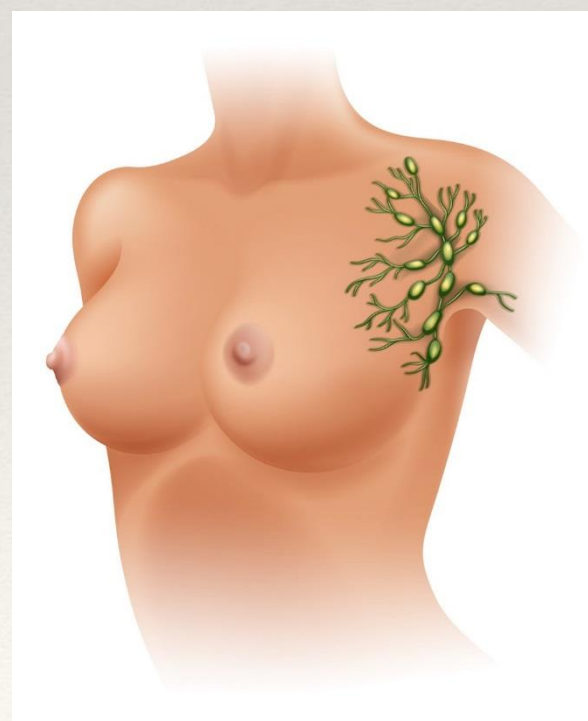
ASIA symptoms (I)

- ❖ Always tired
- ❖ Already tired when waking up
- ❖ Post exertional malaise
- ❖ Wide-spread pain
- ❖ Myalgias and arthralgias
- ❖ Cognitive impairment



ASIA symptoms (II)

- ❖ Pyrexia
- ❖ Sicca symptoms
- ❖ Stroke or MS-like symptoms
- ❖ Raynaud and Livedo reticularis
- ❖ Lymphadenopathy





100 patients evaluated in Maastricht (NL) in 2014 compared with 100 patients evaluated at Baylor College (Houston) between 1985 - 1992

Colaris et al. Immunol Res 2017

Symptom	<u>1994</u> N (%)	<u>2014</u> N (%)	P value
Myalgia, Myositis or muscle weakness	91	54	< .001
Arthralgia, and/or arthritis	81	91	.04
Chronic fatigue, un-refreshing sleep	95	98	.25
Neurological manifestations (especially associated with demyelination)	32	20	.05
Cognitive impairment, memory loss	81	78	.60
Pyrexia	52	64	.09
Dry eyes and/or dry mouth (sicca)	72	73	.87
75% of patients with SBI related ASIA: pre-existent allergies <i>Maijers et al. Neth J med 2013</i>			

- Almost 4300 females with silicone breast implants reported health issues on the World Wide Web
- Prevalence of ASIA is unknown!
- Select group of predisposed (?) women

No studies performed that assessed ASIA symptoms in SBI patients compared to controls.

PATIENT POPULATION

SELECTED PATIENTS

1

143 SILICONE BREAST IMPLANT PATIENTS

- Operated between 1997 – 2004*
- Maastricht University Medical Center, Maastricht; St. Anna Hospital, Geldrop; Maxima Medical Center, Eindhoven
→ The Netherlands

2

94 HEALTHY CONTROLS

- Friends of the patients of group 1
- Age- and sex-matched
- Exclusion criteria: (history of) silicone breast implants and/or (history of) breast cancer.

3

139 SILICONE BREAST IMPLANT PATIENTS

- Previous reported health issues!
- Registered at a Dutch foundation for women with illness due to breast implants
- Matched for the period of breast implantation to group 1.

231 FEMALES

RESPONDED PATIENTS

INCLUDED

N = 222

1

N = 79

2

N = 62

3

N = 81

**Colaris et al. Immunol Res 2017.*

In non-selected SBI patients 4 x more frequent ASIA compared to HC

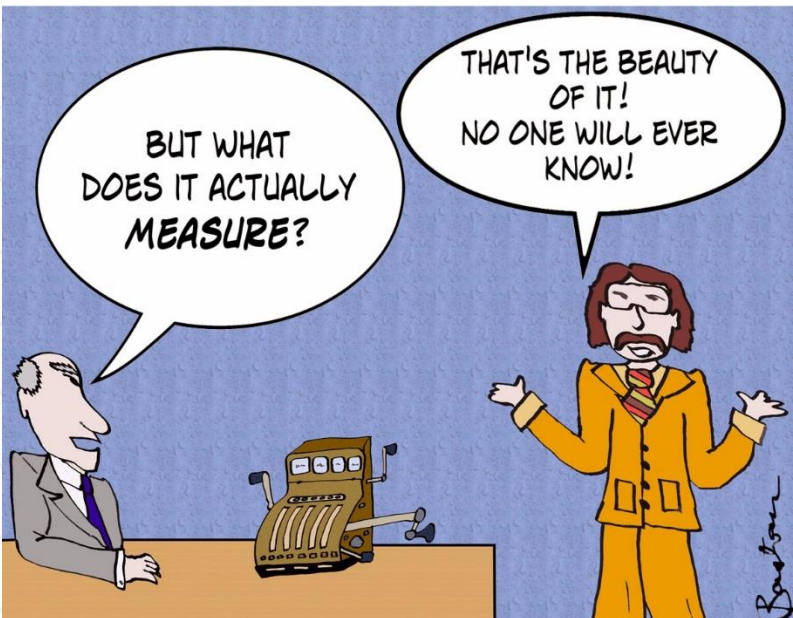
Colaris M, Cohen Tervaert JW. unpublished

	Group 1 SBI patient (n=84)	Group 2 Negative controls (HC) (n=48)	Group 3 Positive controls (MKS) (n=86)
Amount of ASIA symptoms	2.34 ± 1.5	1.8 ± 1.8	4.06 ± 1.5
ASIA (Tree 1)	44 (52%)	14 (29%)	67 (78%)
ASIA (tree 2)	19 (23%)	3 (6%)	46 (53%)

***Tree 1:** Arthralgia and/or myalgia AND fatigue/sleep disturbances*

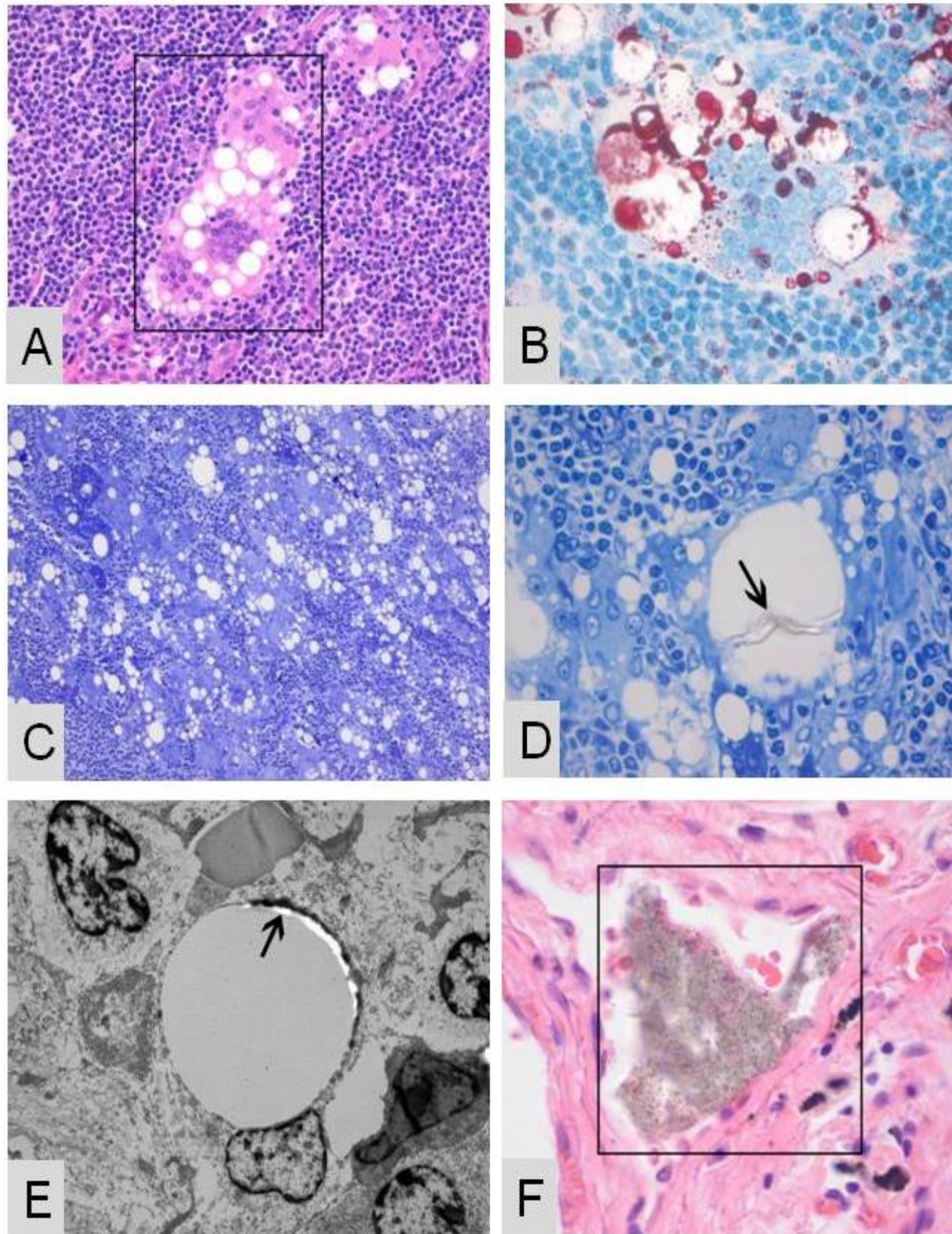
***Tree 2:** Arthralgia and/or myalgia AND fatigue/sleep disturbances
and/or cognitive impairment AND pyrexia and/or sicca*

AN EARLY PROTOTYPE FOR GENERATING
CLINICAL TRIAL OUTCOME SHORTCUTS.



ASIA: Mass somatization ?

Dush DM. ARD 2001



Multiple lymph nodes of patient 1 were filled with large quantities of multinucleated giant histiocytes in presence of possible exogenous material, suggestive of silicone A-E

- Figure A shows a 4 µm paraffin cut stained with Hematoxylin and Eosin
- Figure B shows a 4 µm paraffin cut stained with the MORO, positive stained material is present inside the giant histiocytes
- Figure C shows a 1 µm toluidin blue stain where multiple giant histiocytes are seen in presence of multiple vacuoles
- Figure D shows a higher magnification of the toluidin blue stain where threadlike translucent material is present inside the vacuoles
- Figure E shows a TEM micrographs of a vacuole with dens perivacuolar material

Often material is clearly located inside a bloodvessel, this event can be found throughout all tissues (F)

Gel Bleed and Rupture of Silicone Breast Implants Investigated by Light-, Electron Microscopy and Energy Dispersive X-ray Analysis of Internal Organs and Nervous Tissue
Kappel et al. Clin Med Rev Case Rep 2016, 3:087

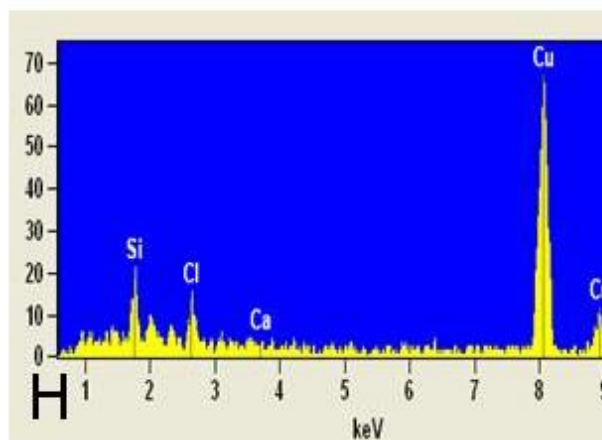
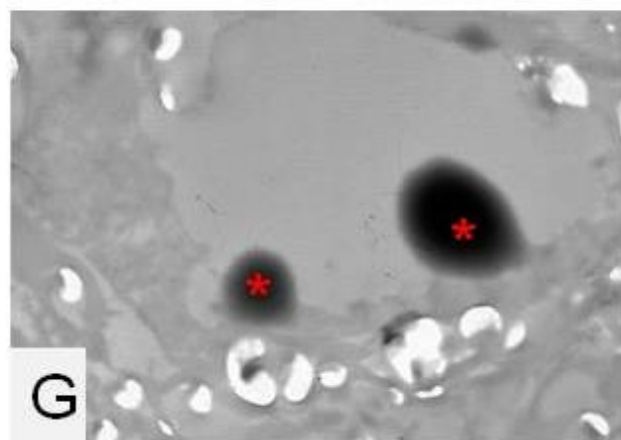
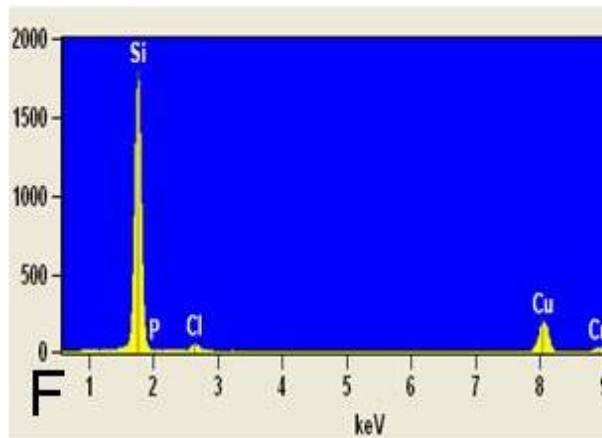
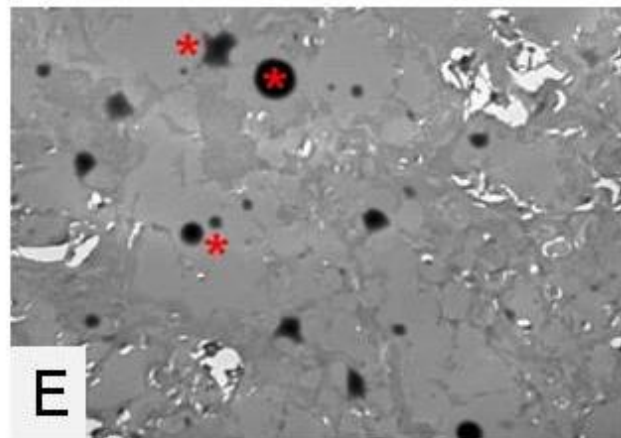
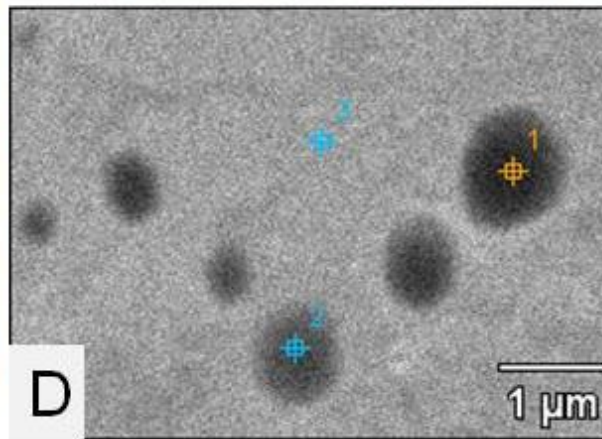
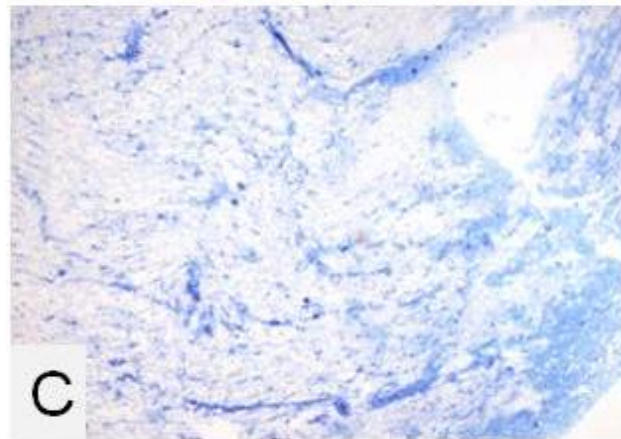
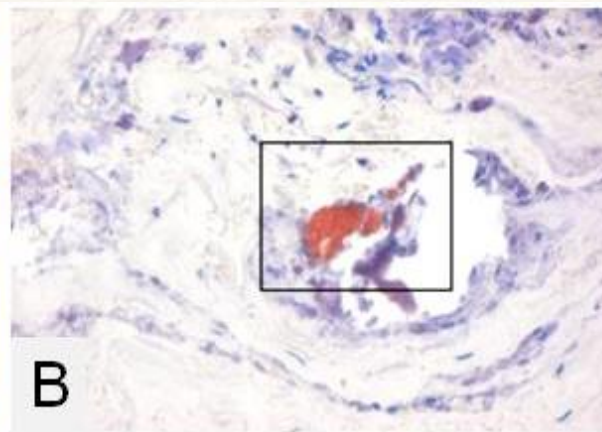
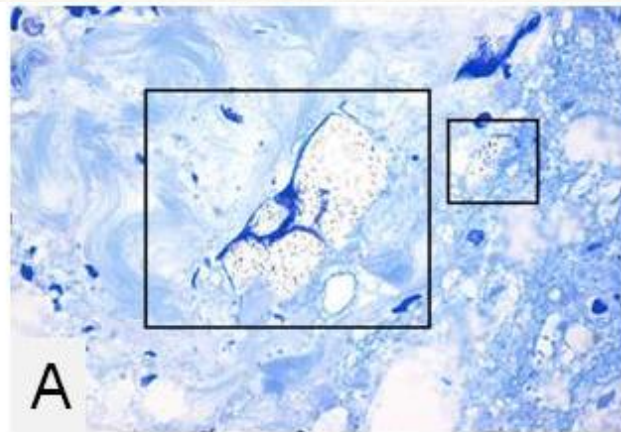


Figure A shows toluidine blue of the **spinal cord** high cervical, clearly visible is a structure surrounded by collagen, same structures often are positive with MORO staining, reddish plaque is visible (B)

Figures D, E and G show the droplets * found in the thoracic spinal cord of patient 1

Figure C shows the toluidine blue stained epon section, no visible droplets are detectable

Figure E shows a TEM micrograph where it is nicely demonstrated that there are actually droplets present

Figure G shows a higher magnification of a TEM micrograph where it is clearly seen that the droplets actually are located inside a vacuole and are part of the tissue

EDX analysis is performed on these droplets, figure D shows a TEM micrograph of the EDX measuring points performed on the thoracic spinal cord of patient 1

Figure F demonstrates EDX analysis Point 1 on a droplet found inside vacuolated spaces (spectra 1) = 22211 Si-counts. Point 3 is on the surrounding tissue (spectra 3) = 195 Si-counts (H)

Silicones present in many many organs
Courtesy of Dr. Kappel

Silicone breast illness

Major Criteria:

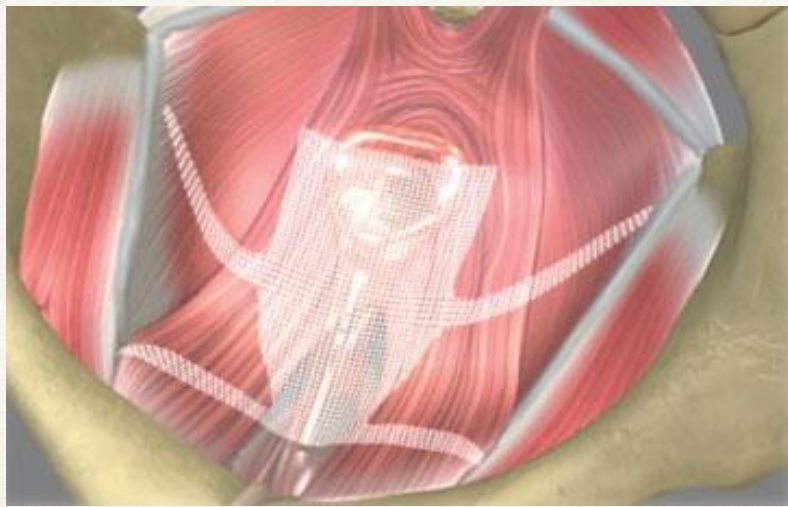
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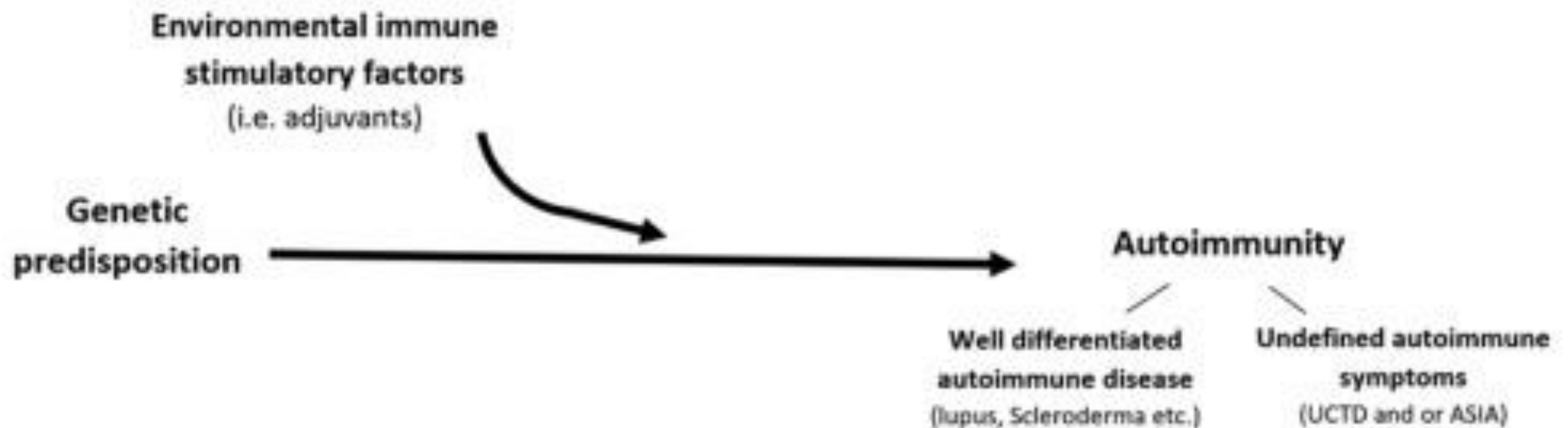
MORE OFTEN
AUTO-IMMUNE DISEASES ?

- ❖ Since 1962 different "names":
 - human adjuvant disease
 - adjuvant breast disease
 - silicone-related symptom complex
 - siliconosis
 - ASIA due to silicone implant incompatibility syndrome
- ❖ Similarities with fibromyalgia
- ❖ Differences:
 1. more often severe sicca
 2. more often immune-deficiency
 3. more often MS-like symptoms and/or CVA/TIA



Foreign body implantation results in adjuvant activity

Babensee JE. 2008

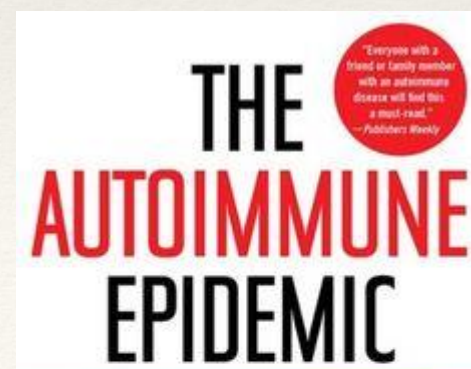


Case Report (I)

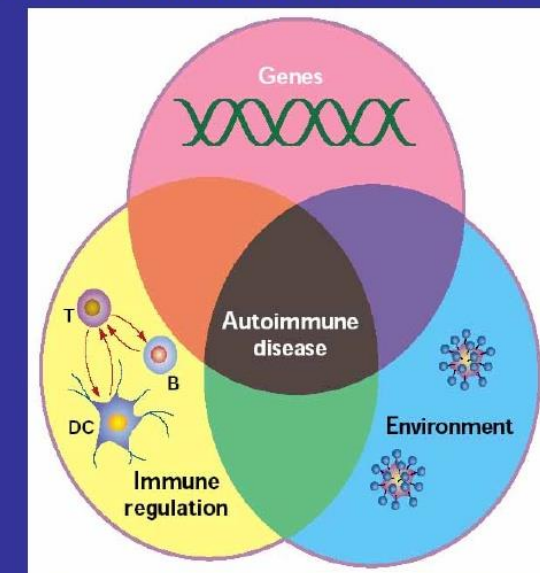
- ❖ 39 year old woman
- ❖ 2006 breast implants; new implants in 2010
- ❖ Since 5 years intermittent fever and fatigue
- ❖ Joint pain and myalgias
- ❖ Sicca complaints
- ❖ Concentration problems
- ❖ "Alzheimer-light"
- ❖ Recent onset Raynaud



Is the risk of an auto-immune disease in SBI patients increased ?



Requirements for the development of an autoimmune disease



Nature Immunology (9): 759-761 (2001)

What about animal studies ?

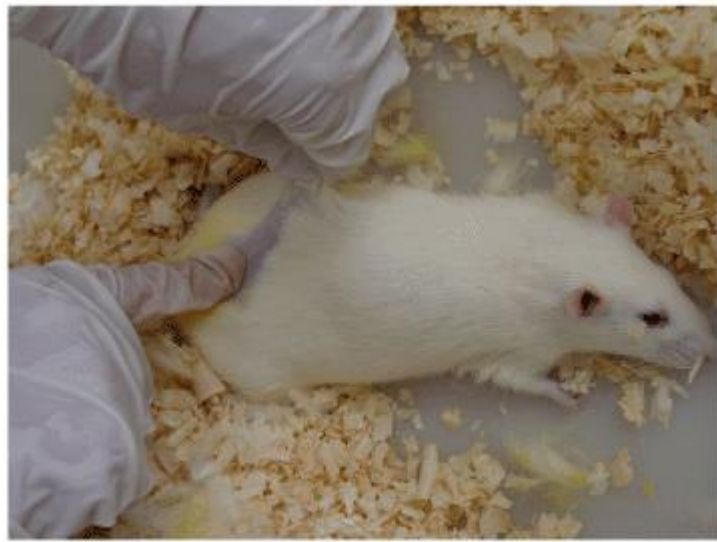


FIGURE 3 - The fur is cleared from the incision area.

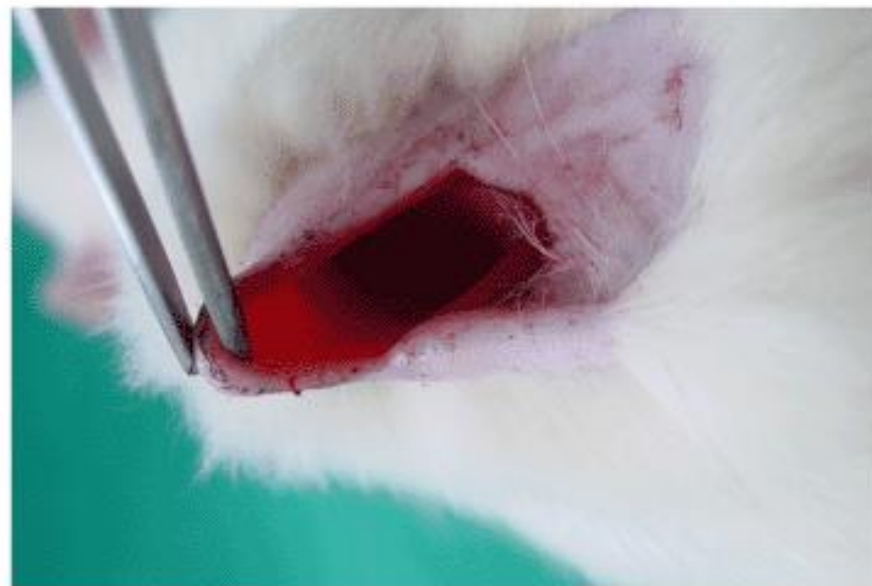


FIGURE 6 -Dissected tunnel.



FIGURE 7 – Smooth minimplants being introduced.

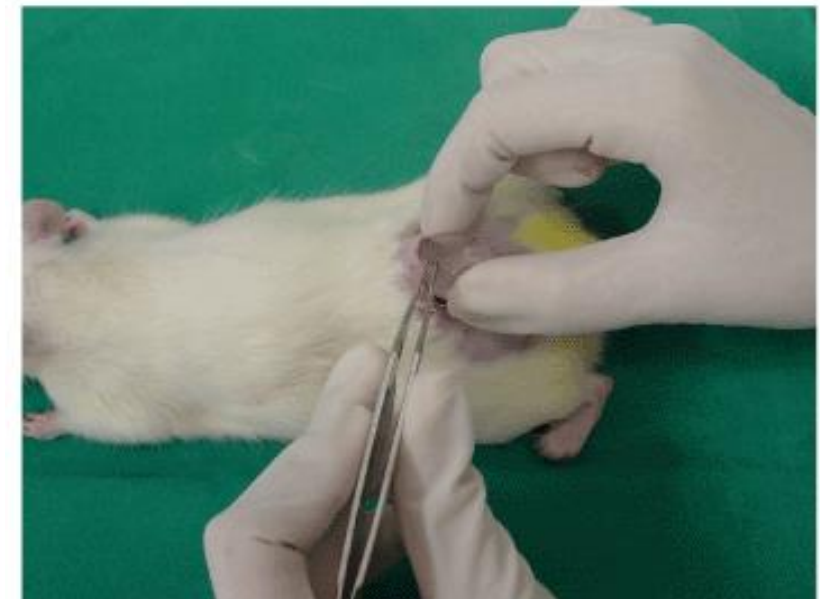


FIGURE 8 - Textured implant being introduced.

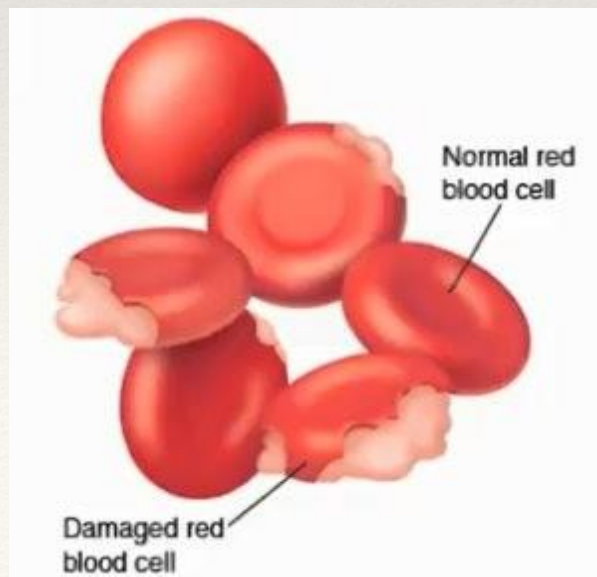
No evidence of AIZ in several rat and/or mice models



BUT.....

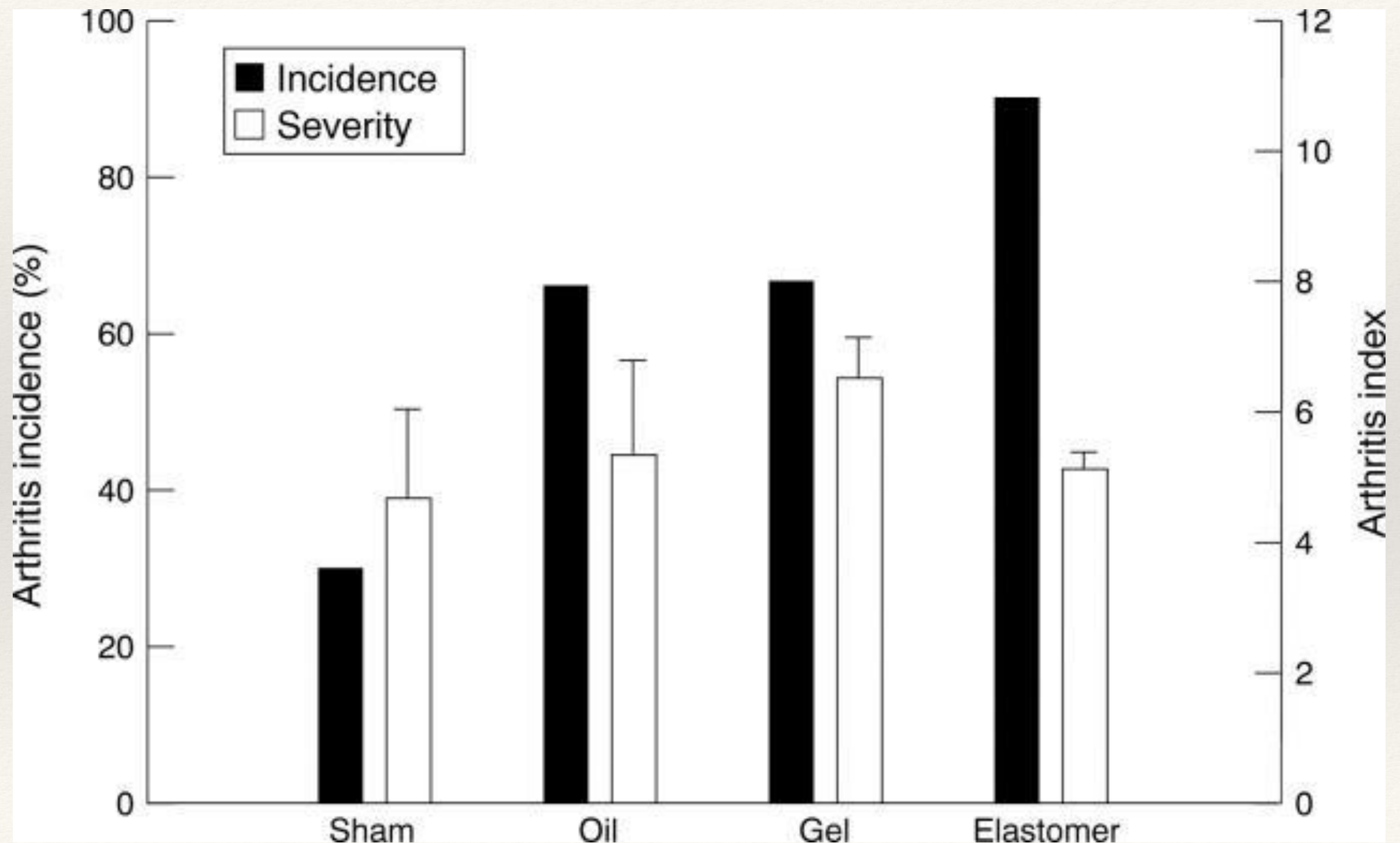
Silicone gel enhances AIZ in NZB but not in BALB/c mice

McDonald et al. Clin Immunol Immunopath 1998



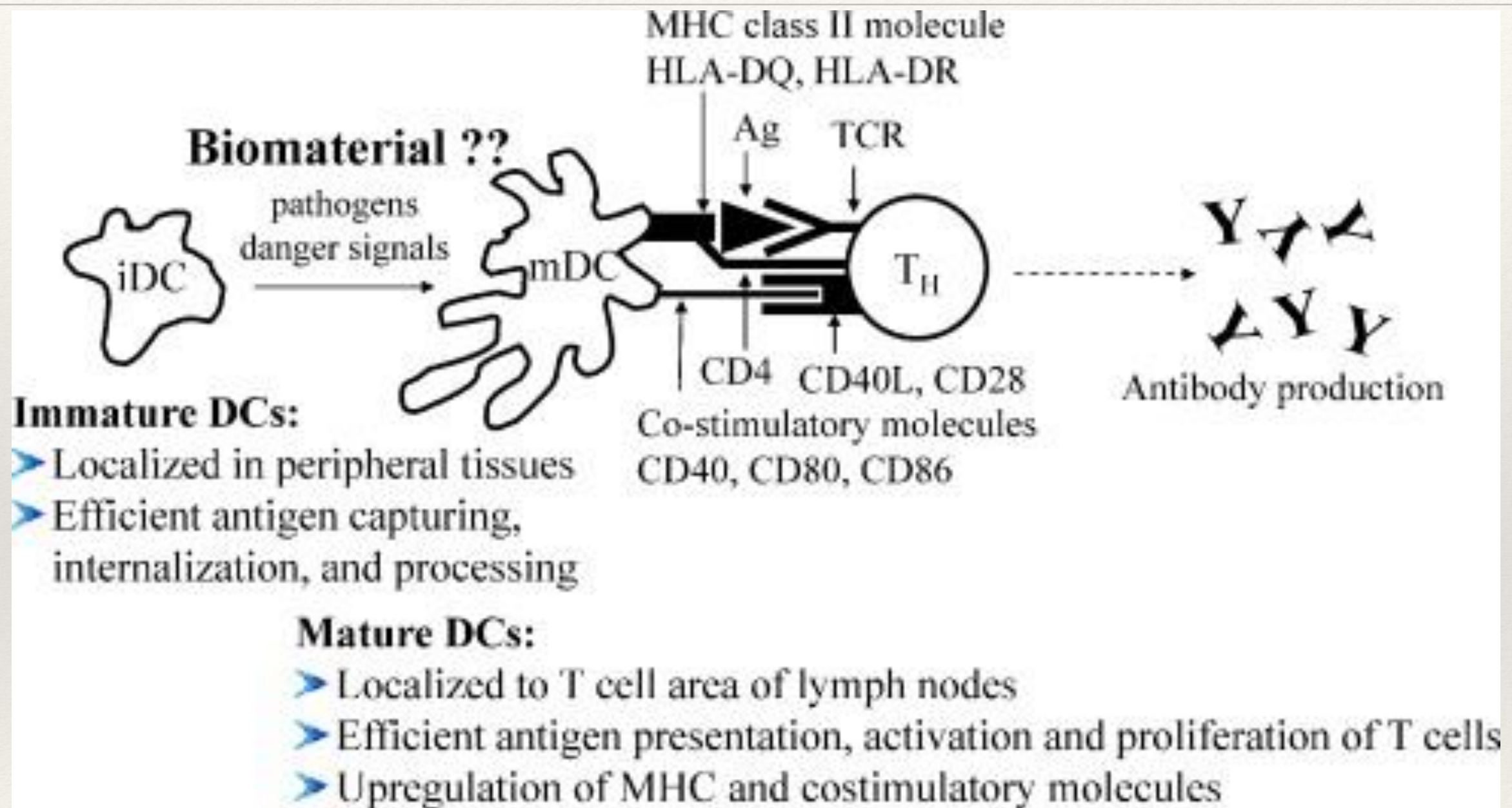
Long-term Silicone implantation on type II collagen induced arthritis in mice

Schaefer et al. ARD 1999



Biomaterials induce adjuvant activity

Babensee JE. Sem Immunol 2008



What about AIZ and other immunologic complications in our patients ?

Clinical diagnoses in 32 patients with ASIA due to SIIS (n = 32)

Cohen Tervaert et al. Immunol Res 2013

- ❖ Median time between implantation and complaints:
10 years (2 - 24 years)
- ❖ 8 patients : Biopsy-proven siliconosis
- ❖ 2 patients : Non-Hodgkin Lymphoma
- ❖ 15 patients : immune deficiency
(8 x CVID; 7 x IgG subclass deficiency)
- ❖ 17 patients : systemic AI disease
- ❖ 7 patients : organ specific AI disease

Autoimmune diseases in ASIA due to SIIS

Cohen Tervaert et al. Immunol Res 2013

- ❖ 6 patients systemic necrotizing vasculitis
- ❖ 6 patients CTDs:
 - 2 x APS; 2 x Sjogren; 1 x SSc; 1 x SLE
- ❖ 4 x granulomatous disease:
 - 3 x sarcoidosis; 1 x Crohn's disease
- ❖ 1 x multiple sclerosis
- ❖ 4 x pernicious anemia
- ❖ 3 x hypothyroidism

Large cohort:

Autoimmune diseases in 100 consecutive patients with SBI induced ASIA

Colaris et al. Immunol Res: 2017

❖ RA	4
❖ CTD	18
❖ Vasculitis	5
❖ Granulomatous disorders	3
❖ Other AID	7

*Silicones in breast implants
NO INCREASED RISK ???*

Silicones in breast implants

NO INCREASED RISK ???

Recent meta-analysis study

Balk et al. Ann Int Med 2016

Nearly all previous studies:

not adequately adjusted or not adjusted for potential confounders

Decreased risk for breast and endometrium cancer,
increased risk for lung cancer



Increased risk for:
RA (RR 1.38; CI, 1.06 - 1.80)
SS (RR 2.92; CI, 1.01 - 8.47)



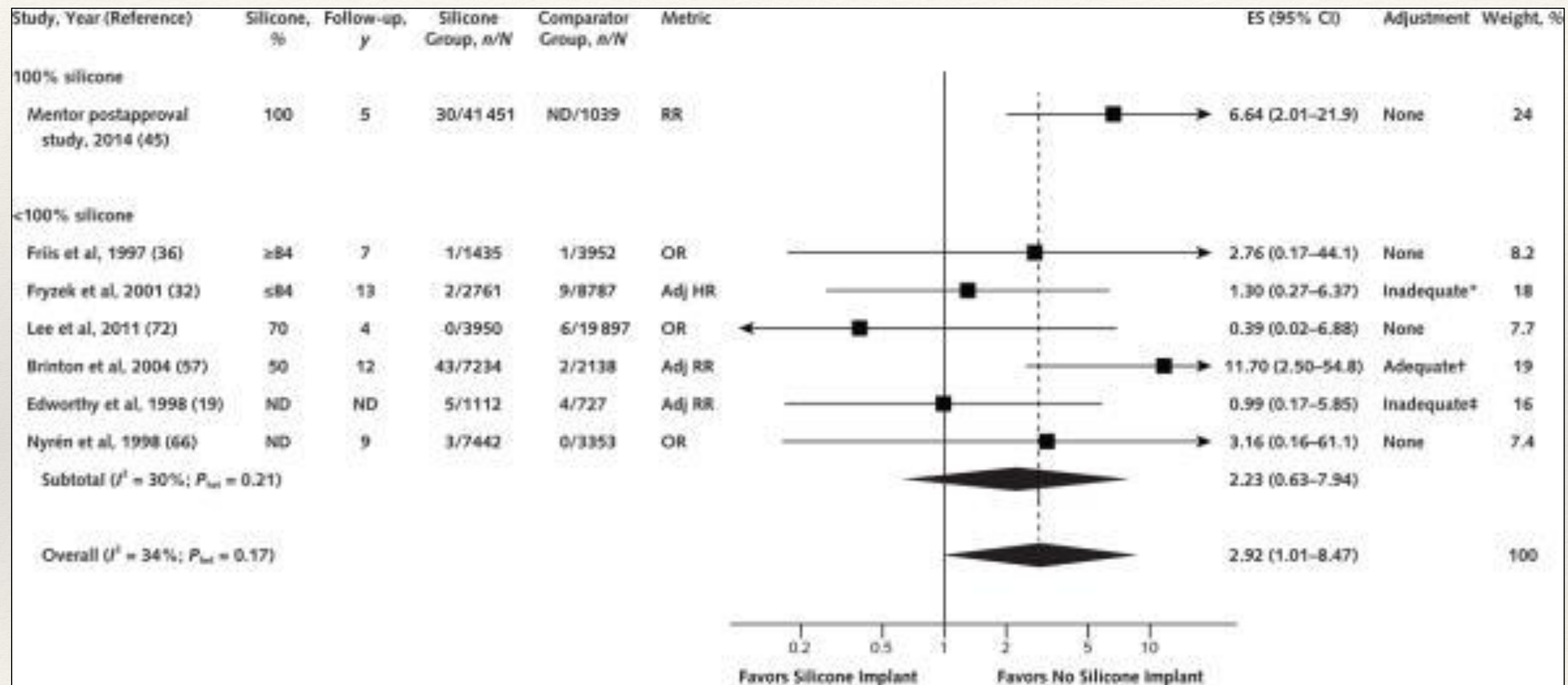
Associations mainly driven by self-reported disease

Conclusion: epidemiological studies **inconclusive**

Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review.

Balk, Ethan; MD, MPH; Earley, Amy; Avendano, Esther; Raman, Gowri; MD, MS

Annals of Internal Medicine. 164(3):164-175, February 2, 2016.



Relative Risk for Sjogren Syndrome (RR 2.92; CI, 1.01 - 8.47)

TABLE 3

FDA Breast Implant Postapproval Studies: Long-term Outcomes in 99,993 Patients.

Coroneos, Christopher; MD, MSc; Selber, Jesse; MD, MPH; Offodile, Anaeze; II MD, MPH; Butler, Charles; Clemens, Mark

Annals of Surgery. 269(1):30-36, January 2019.

DOI: 10.1097/SLA.0000000000002990

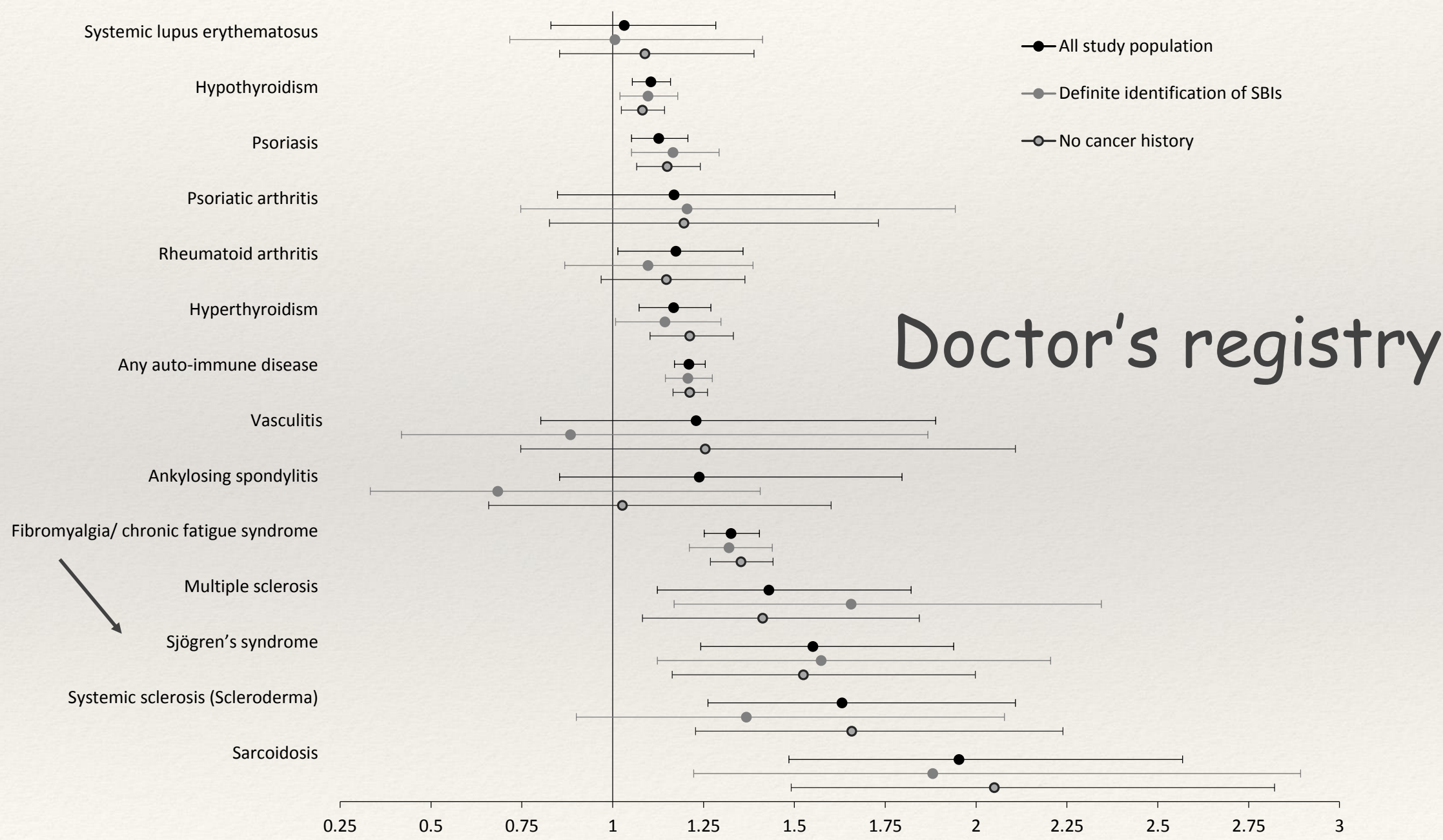
	Manufacturer ^{*,†}	Study Events	Study Event Rate (Per 10,000 Person Yr)	General Population Event Rate (Per 10,000 Person Yr)	SIR	SIR 95% CI	P Value
Fibromyalgia	Allergan	9	1.8	112.8	0.02	0.01–0.03	<0.001
	Mentor	307	28.4	112.8	0.25	0.22–0.28	<0.001
Rheumatoid arthritis	Allergan	4	0.8	5.4	0.15	0.04–0.38	<0.001
	Mentor	349	32.2	5.4	5.96	5.35–6.62	<0.001
Scleroderma	Mentor	46	4.2	0.6	7.00	5.12–9.34	<0.001
Sjogren syndrome	Mentor	62	5.7	0.7	8.14	6.24–10.44	<0.001
Systemic lupus erythematosus	Allergan	3	0.6	5.4	0.11	0.02–0.32	<0.001
	Mentor	66	6.0	5.4	1.11	0.86–1.41	0.398
Cancer	Allergan	80	16.0	41.3	0.39	0.31–0.48	<0.001
	Mentor	532	63.8	41.3	1.54	1.42–1.68	<0.001
Breast cancer	Mentor	116	13.9	12.5	1.11	0.92–1.33	0.26
Lung cancer	Mentor	5	0.6	5.2	0.12	0.04–0.27	<0.001
Brain cancer	Mentor	3	0.4	0.6	0.67	0.14–1.95	0.639
Melanoma	Mentor	65	7.8	2.1	3.71	2.87–4.73	<0.001
Neurological disorder	Allergan	18	3.6	22.5	0.16	0.09–0.25	<0.001
	Mentor	394	35.8	22.5	1.59	1.44–1.76	<0.001
Multiple sclerosis	Mentor	47	4.3	2.5	1.72	1.26–2.29	0.001
Myositis	Mentor	17	1.5	0.8	1.88	1.09–3.00	0.018

*Allergan follow-up 2 years.
†Mentor follow-up 7 years.

24,651 SBI recipients and 98,604 matched SBI free women adjusted OR for AD 1.21, 95% CI 1.17-1.26

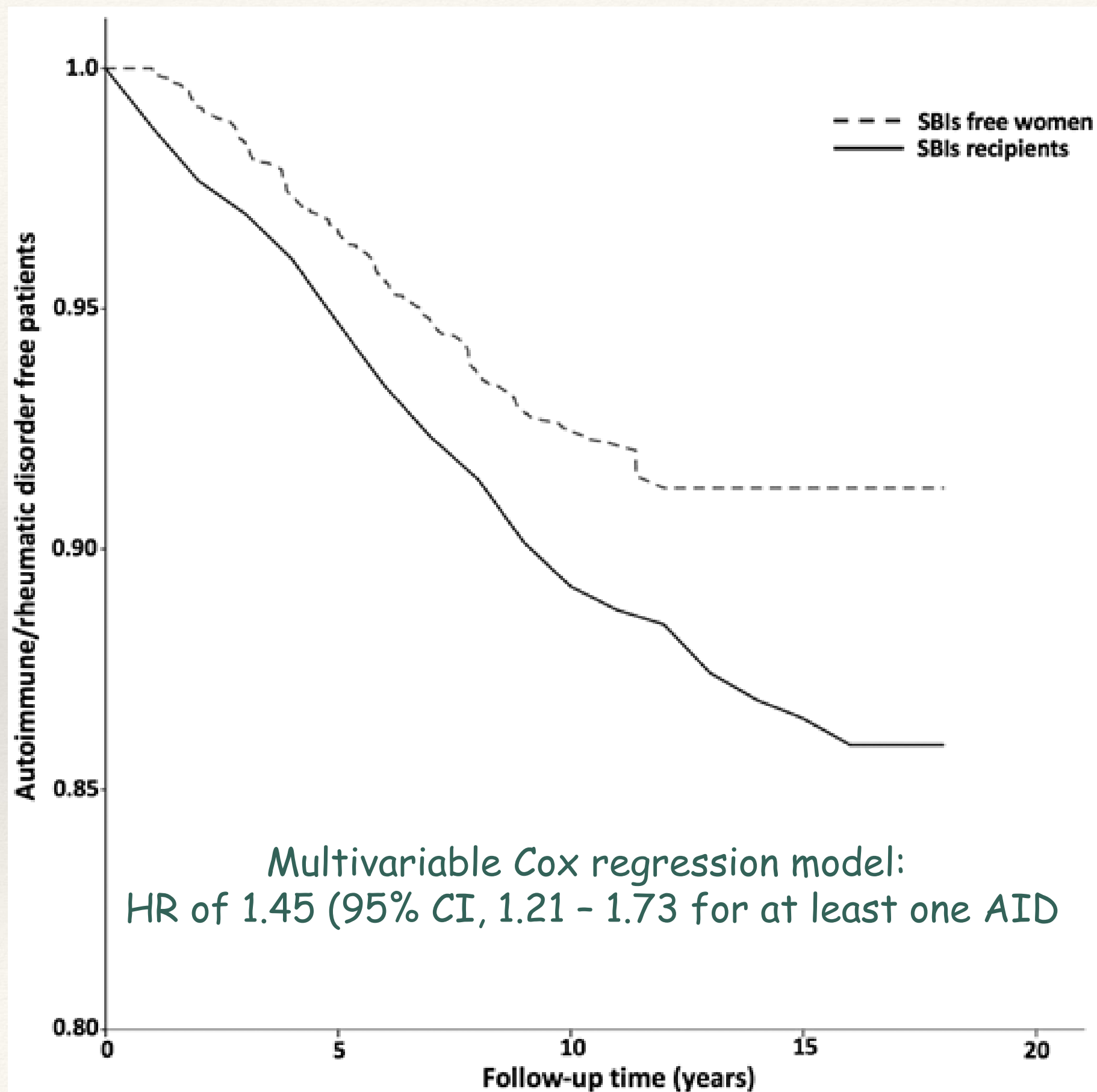
Figure 2. Adjusted* odds ratios (95% confidence interval) for auto-immune diseases among SBI recipients in comparison to SBI-free women in 3 different multivariate analysis

*Adjusted for: age ; socio-economic status ; birth place ; smoking status; breast



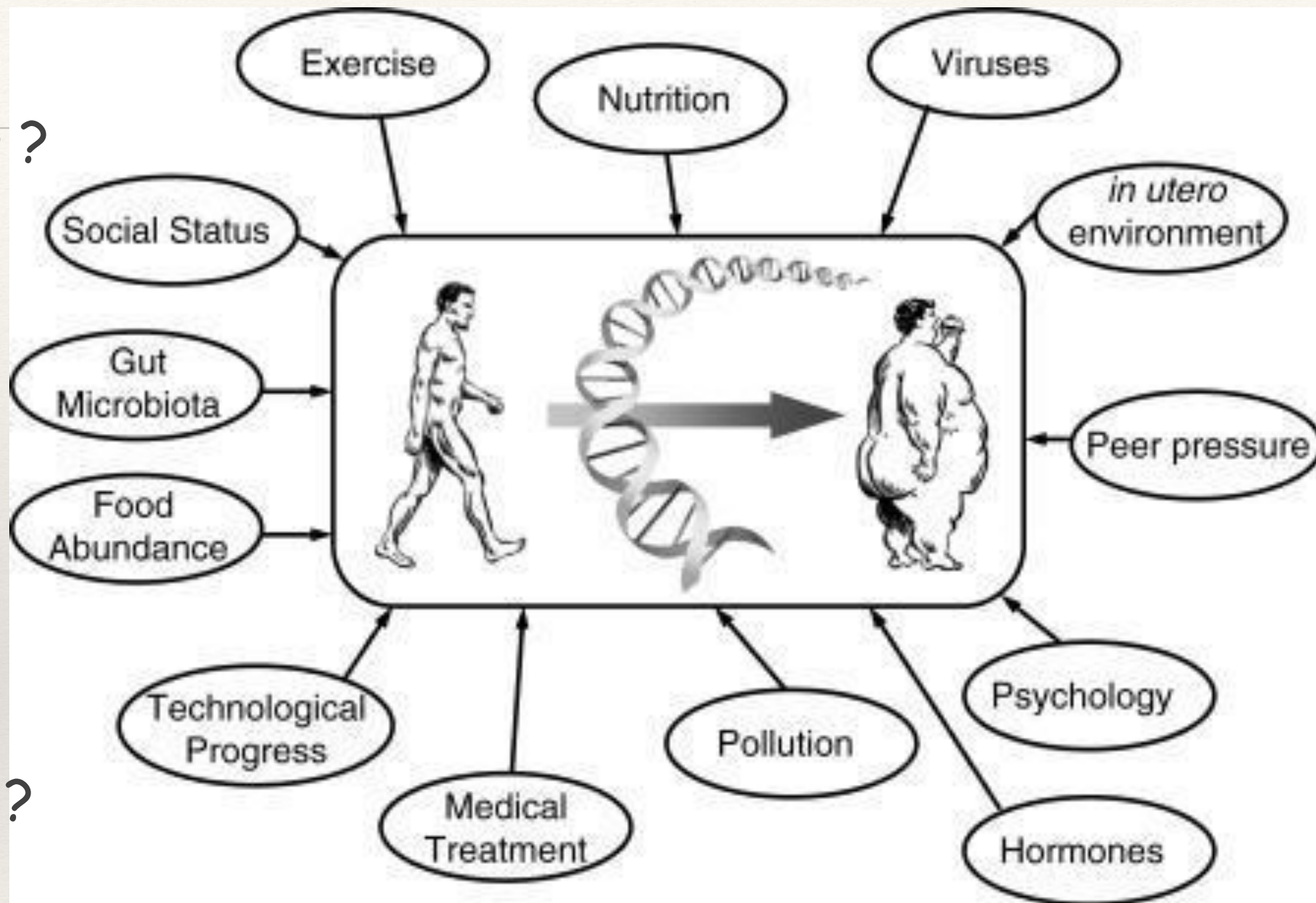
Large recent study from Israel

Watad et al. 2018



Vitamin D deficiency IgG deficiency Bacterial and viral infections

Smoking ?



Salt ?

Stress ?

AID

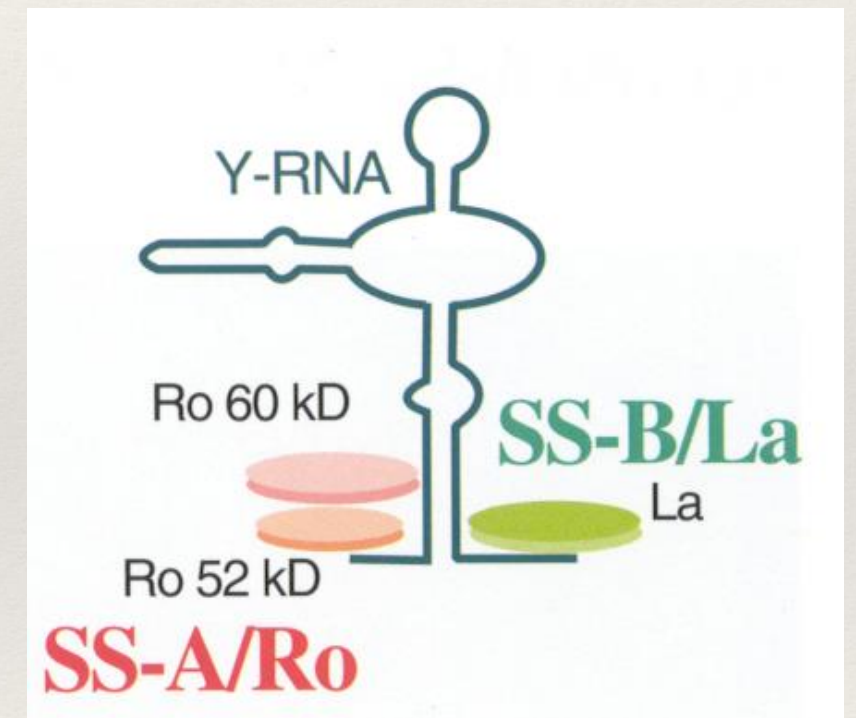
Granulomatous inflammation

Metal allergy

Adjuvant effect of silica

Case report II: Laboratory results

- ❖ ANA: pos 1: 80; SSA: pos; SSB neg
- ❖ Creat: 73; sed: no abnormalities
- ❖ ALAT:18; HCV: neg
- ❖ Cryoglobulin: negative



Silicone-induced ASIA: therapy ?

- ❖ Non-invasive therapy:
 - symptomatic (e.g., pregabalin)
 - immunosuppressive therapy (e.g., hydroxychloroquin)

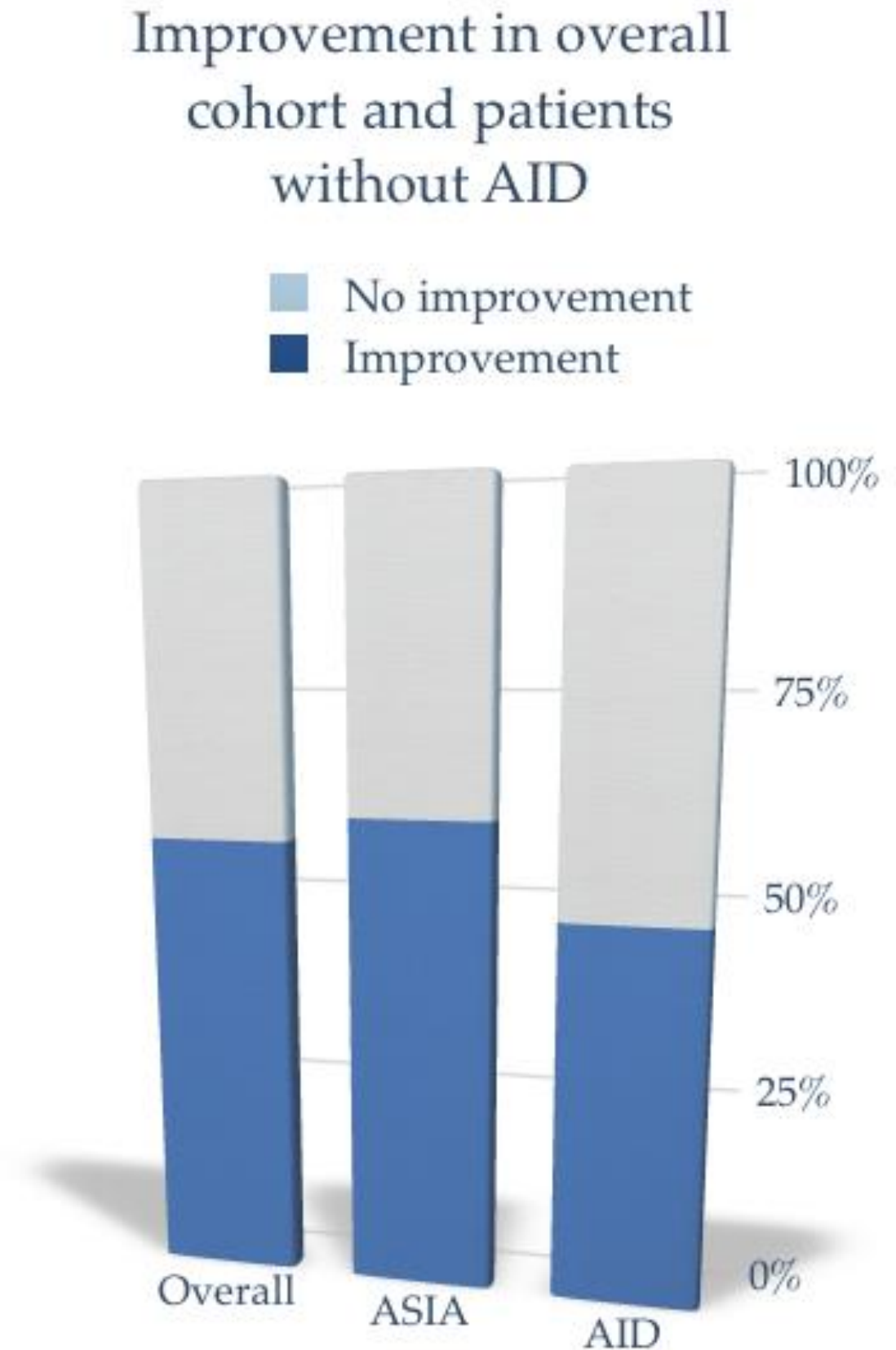
- ❖ Invasive therapy
Explantation:
 - Effectivity: 50-75%
 - Recent review 469 of 622 (75%) patients;
in AID effective in only 16% without additional immunosuppressive therapy

Post-explantation Improvement

Patients in Overall ASIA-Cohort:
56% of 85 patients improve (N= 48)

Patients without a well defined auto-immune disease (AID)
60% of 62 patients improve (N= 37)

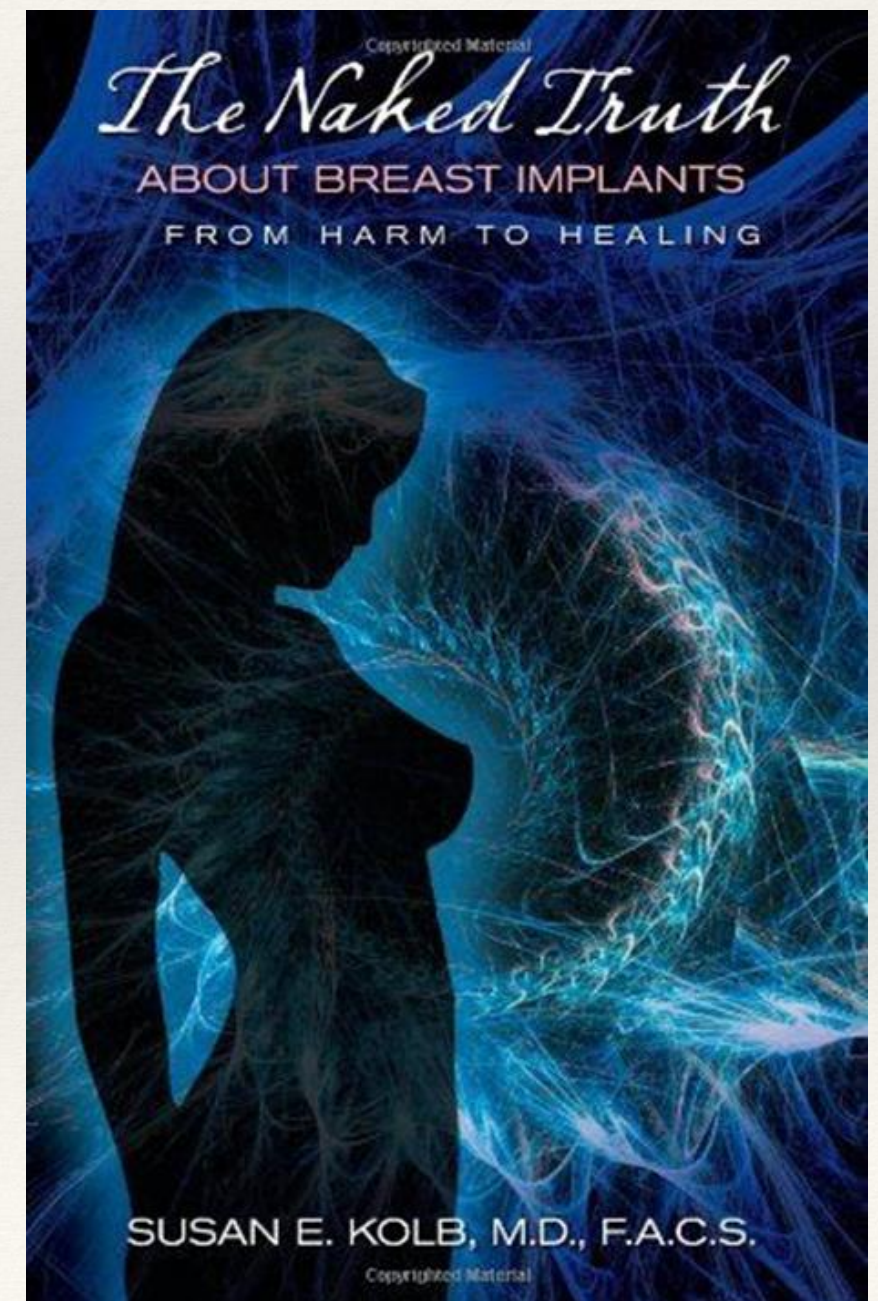
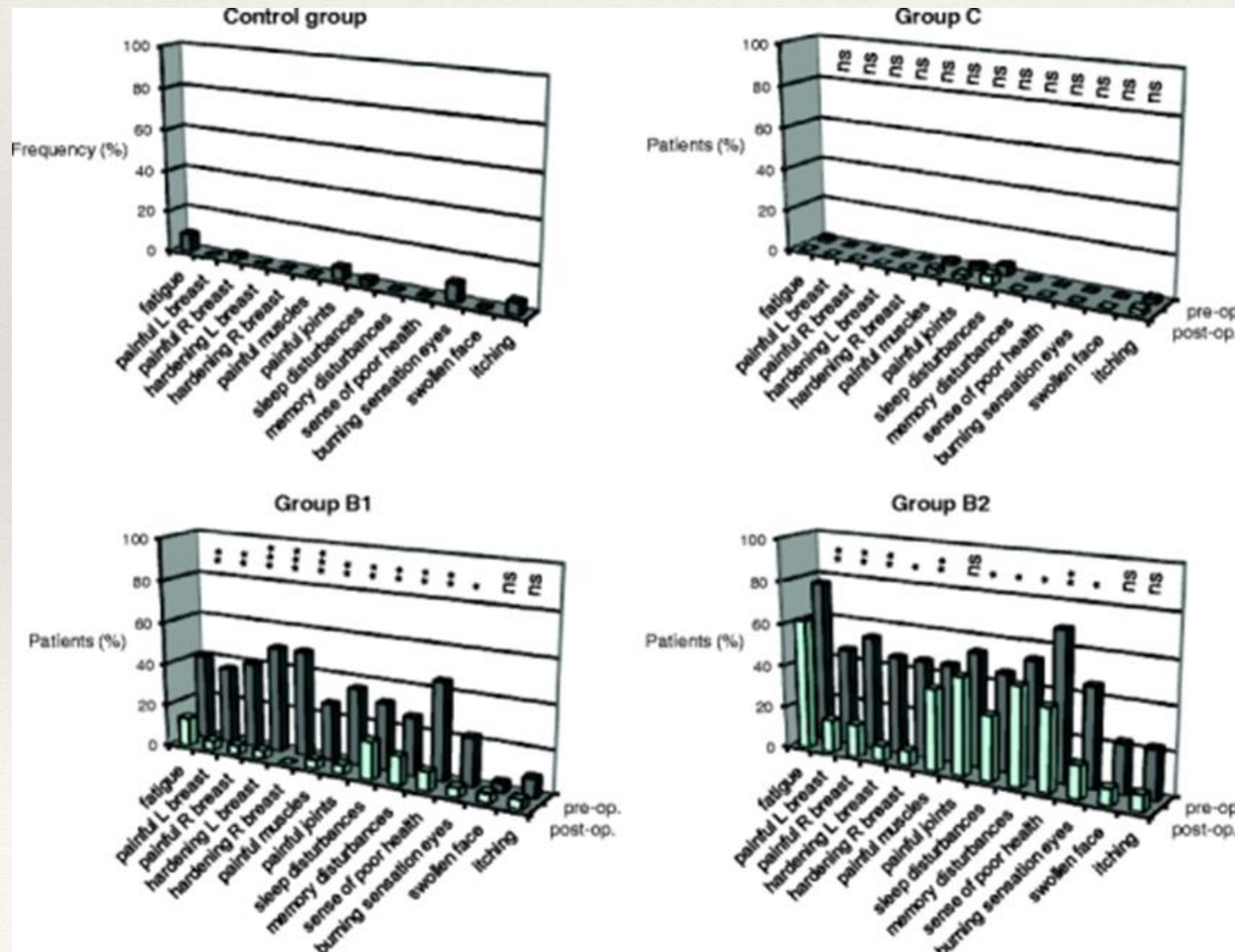
Patients with a well defined auto-immune disease (AID)
48% of 23 patients improve (N = 11)



- ❖ Carbomer gel eyedrops
- ❖ Vitamin D suppletion
- ❖ Silicon-breast removal with capsulectomy

Case report

Kappel et al. Eur J Plast Surg 2012
Cohen Tervaert et al. Immunol Res 2013



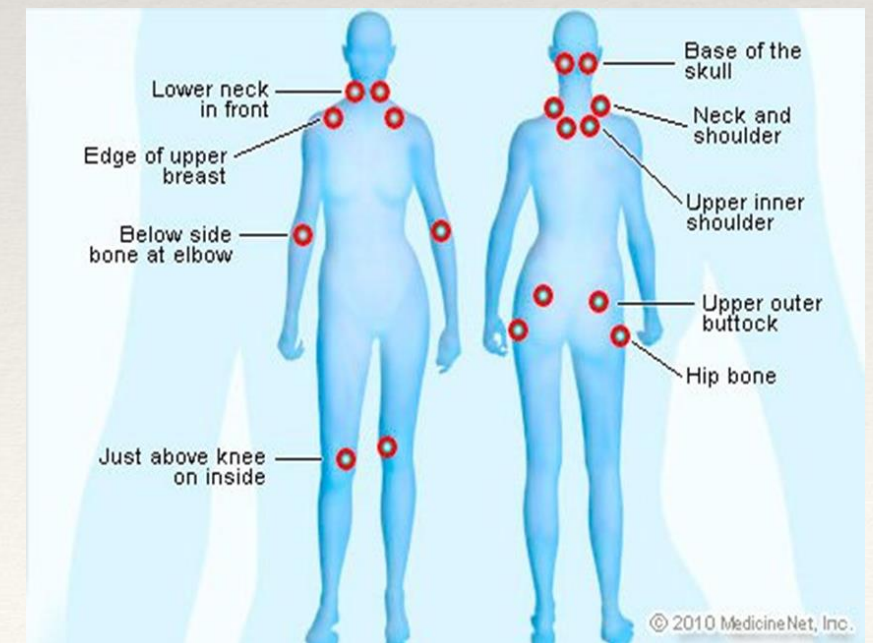
Case report

- ❖ Deterioration after surgery for which (temporarily) steroids were given
- ❖ Start doxycyclin maintenance therapy
- ❖ No fever anymore; 24 months follow-up



Conclusion

- ❖ Biomaterial implantation can result in systemic symptoms with signs of immune activation and/or recurrent infections as a result of immune deficiency
- ❖ Patients with systemic symptoms often have pre-existent allergy, fibromyalgia and/or a pre-existent auto-immune disease



Take Home Messages

- ❖ Silicone breast implants, mesh and mineral oil fillers may cause ASIA
- ❖ In these patients more often immunodeficiency, severe allergies, auto-immune diseases and (possibly) also lymphomas
- ❖ Explantation of the SBI results in 75% of cases in decrease of symptoms

SECOND INTERNATIONAL SUMMIT ON HUMAN GENOME EDITING

27-29 November 2018

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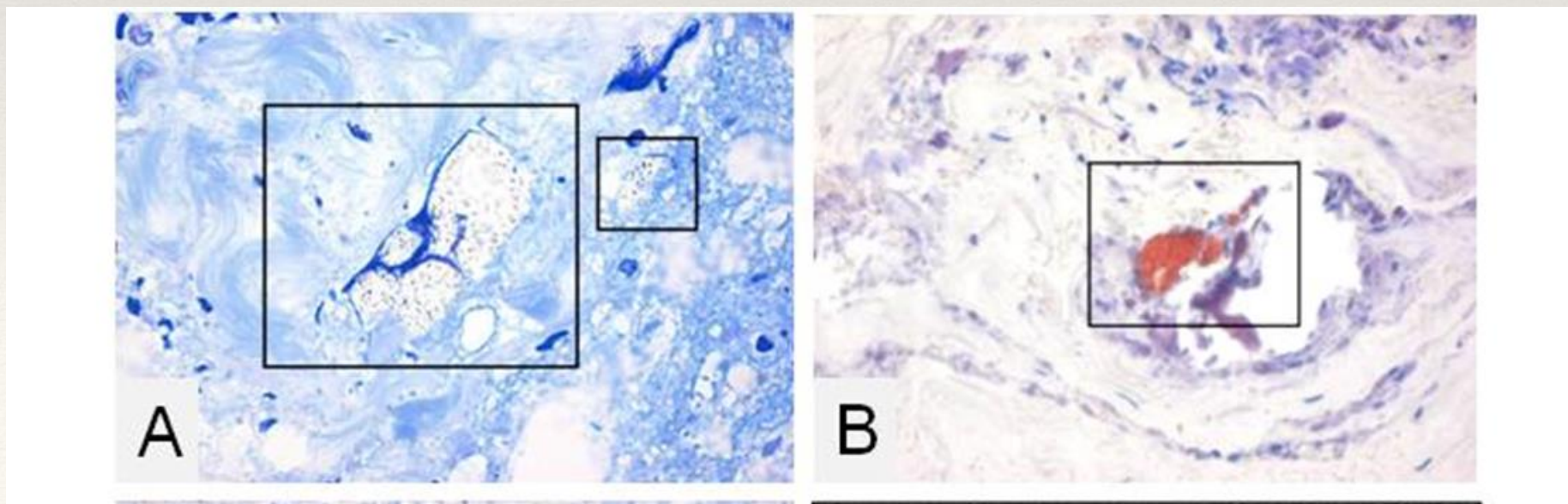


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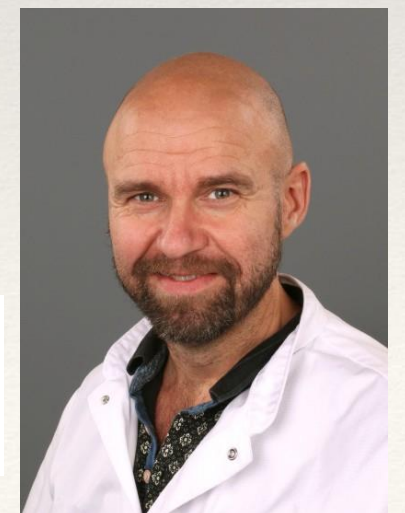


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Dr. Rita Kappel



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Thank you for your attention

Don't go yet