

What might the studies using the
beryllium patch test and the
BeBLPT be telling us?

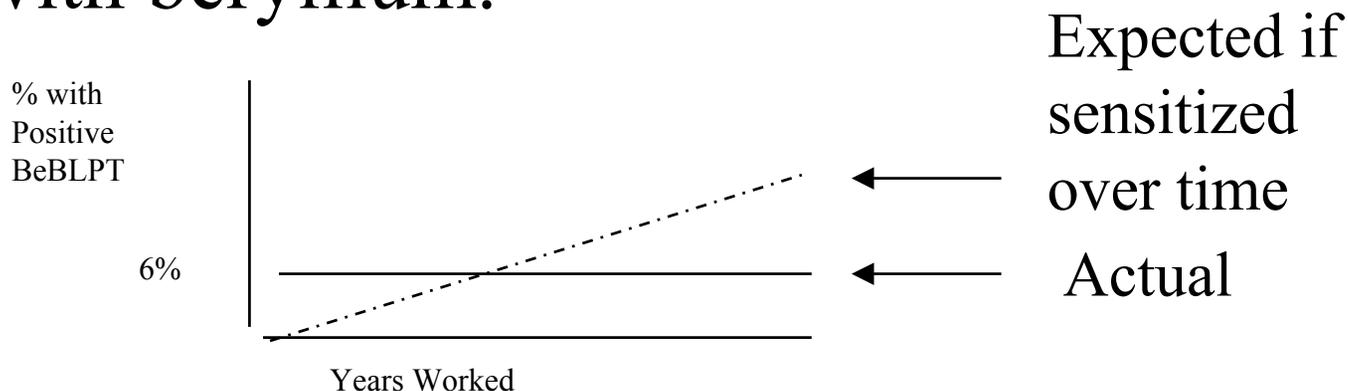
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DOE Beryllium Committee

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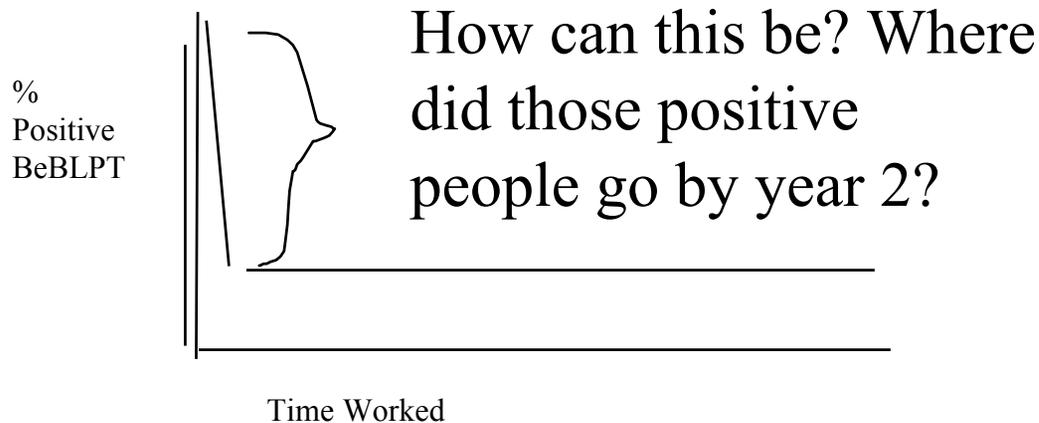
Prevalence studies using the BeBLPT: An enigma

- In the largest prevalence survey of beryllium workers Kreiss and others (1997) found the rate of positive BeBLPT was level over a wide range of years worked with beryllium.



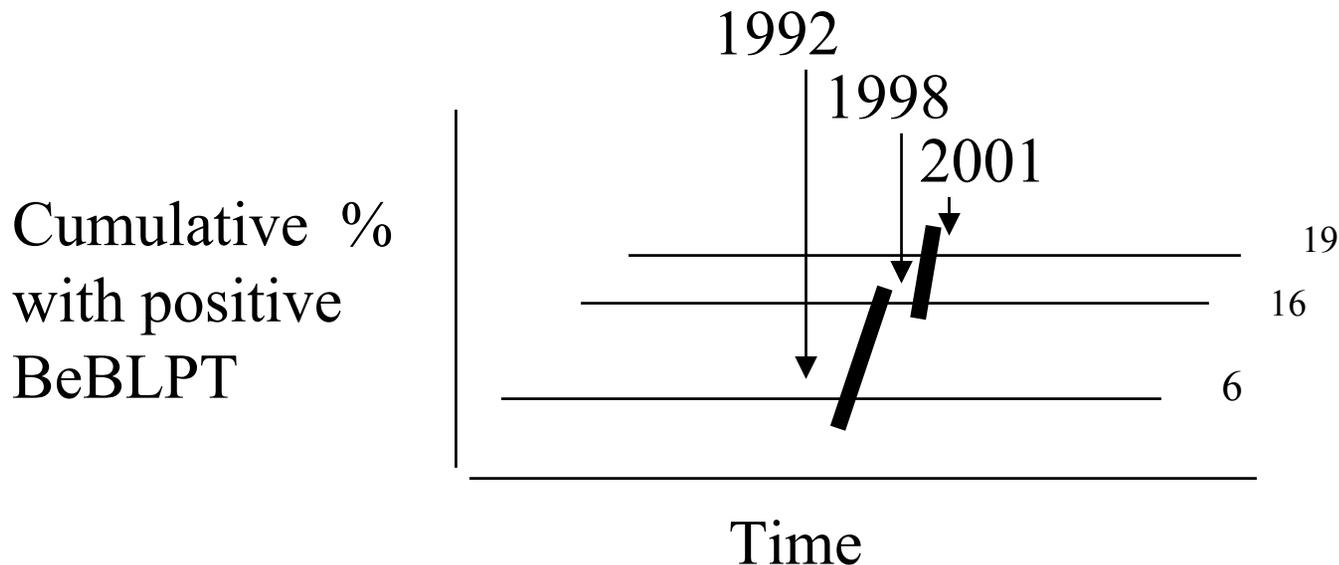
BeBLPT enigma

- In the Tuscon 1998, Elmore 1999 and Reading 2000 surveys we learned that people between 4 and 8 months of employment had a much higher prevalence of positive BeBLPTs



BeBLPT enigma

- Through two surveys and ongoing testing, the cumulative % rises with time while the prevalence in each survey remains flat



BeBLPT enigma: Answer

- You can get a rising cumulative percentage (cumulative incidence) and a flat prevalence in three ways
 - Persons who become BeBLPT positive are removed from the population, e.g. people get sick and choose to leave work, *or*
 - Being BeBLPT positive is a temporary (but possibly recurring) condition, e.g. people switch from negative to positive to negative, *or*
 - Both of the above

Can the Beryllium patch test (BePT) literature help us understand this?

- Curtis 1951: Cleveland Clinic dermatologist
 - At least 8 of 16 volunteers (50%) developed positive BePTs on one application of multiple beryllium salts to the skin
- Shima 1973: Doctor working with NGK
 - Experienced beryllium workers gave 100% positive BePTs (beryllium salt)
 - Up to 80% of new workers with highest exposures developed positive BePTs in the first year of work

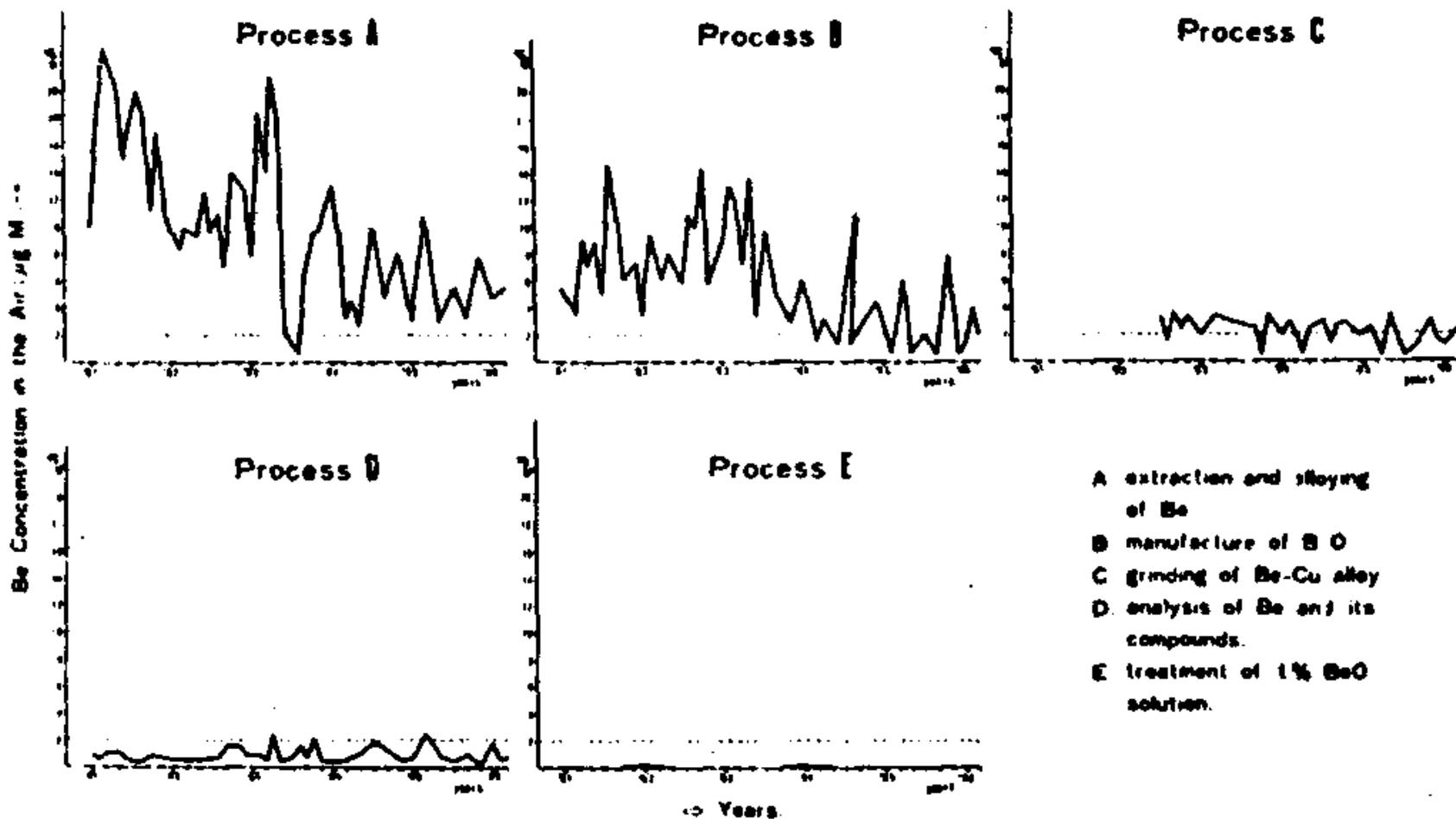
Sensitization via the Skin: Beryllium Patch Test: Curtis 1951

BeF2	0.38	0.19	0.019
Example	g Be/ 100 ml	g Be/ 100 ml	g Be/ 100 ml
Control			
Initial BePT	0	0	0
72 H			
Subsequent	2+	0	0
flare-up @			
16 days			
Second	-	3+	1+
BePT 72 H			

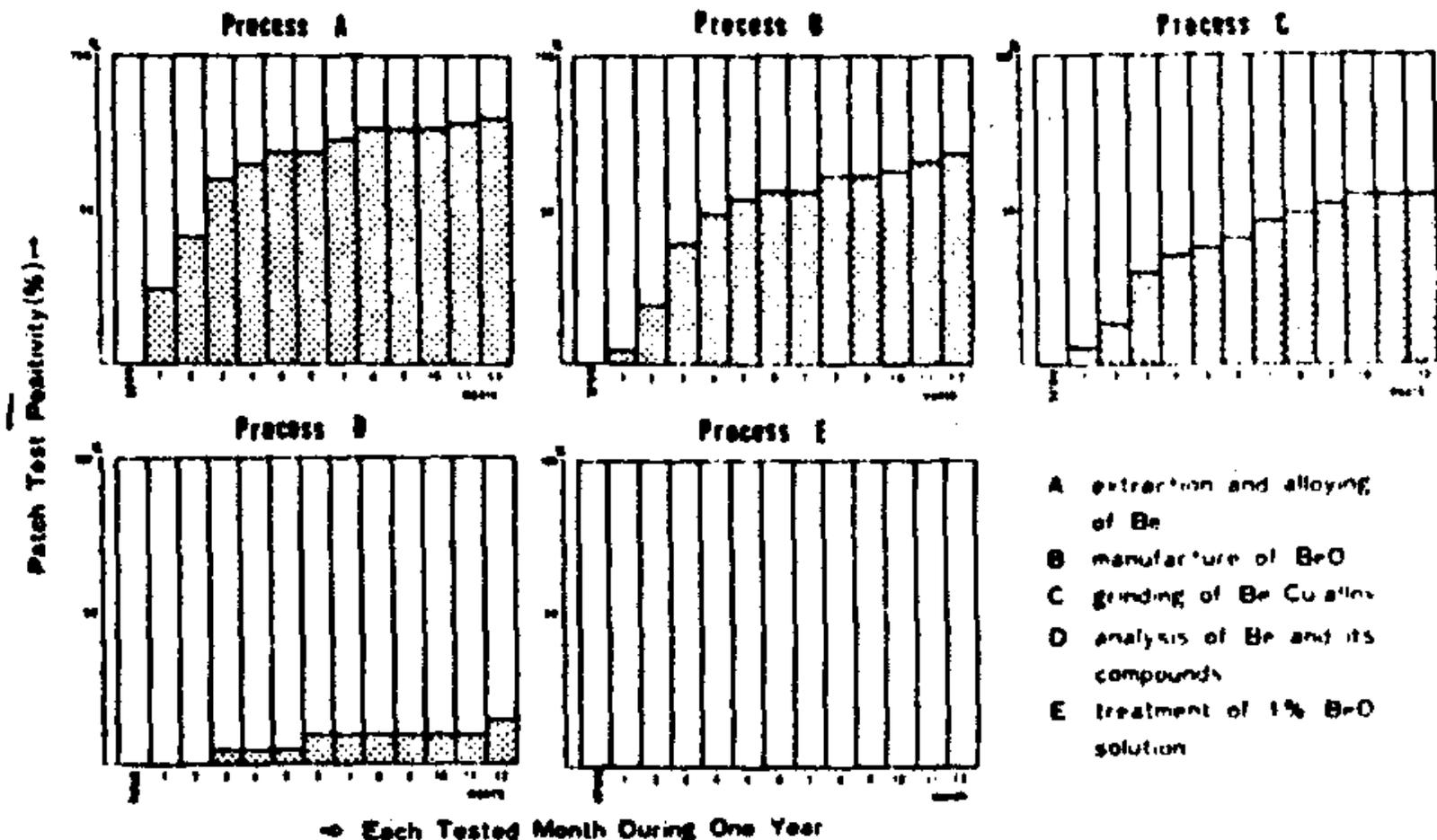
Prevalence: BePT responses in beryllium exposed and unexposed

- Be workers
 - Be Dermatitis 100% (13/13, 0.38% Be Curtis 1951)
 - Be Exposed 100% (80/80, 0.07% Be Shima 1974)
- Non-Be workers
 - 2.5% (1/40, 0.07% Be Shima 1974)
 - 5% (1/20, 0.08% Be Bobka 1997)

A) Beryllium air concentration in each working process



B) Patch test positivity for healthy Be workers in each working process during one year.



Value of the BePT and the BeBLPT

- Primary immune response
 - BePT: Good sensitivity and specificity
 - BeBLPT: Poor sensitivity and very good specificity
- CBD
 - BePT: Poor positive predictive value in Be workers
 - BeBLPT: Good positive and negative predictive value in Be workers

Beryllium immune response

- The BeBLPT may be viewed as a marker of immune activation, or “up-regulation” of the immune response.
- The BeBLPT is an unreliable indicator of beryllium exposure and sensitization, but when positive is a relatively good indicator of the likelihood of CBD
- The BePT is a good indicator of beryllium exposure and subsequent sensitization, but not of who is likely to have CBD

BeBLPT in groups without definite exposure to beryllium

- When most persons in the group have not had exposure to beryllium, a high proportion of BeBLPT positive persons represent the population background rates (false positives) and the BeBLPT has a lower positive predictive value for CBD
- This occurs in the DOE testing

Beryllium exposure and sensitization

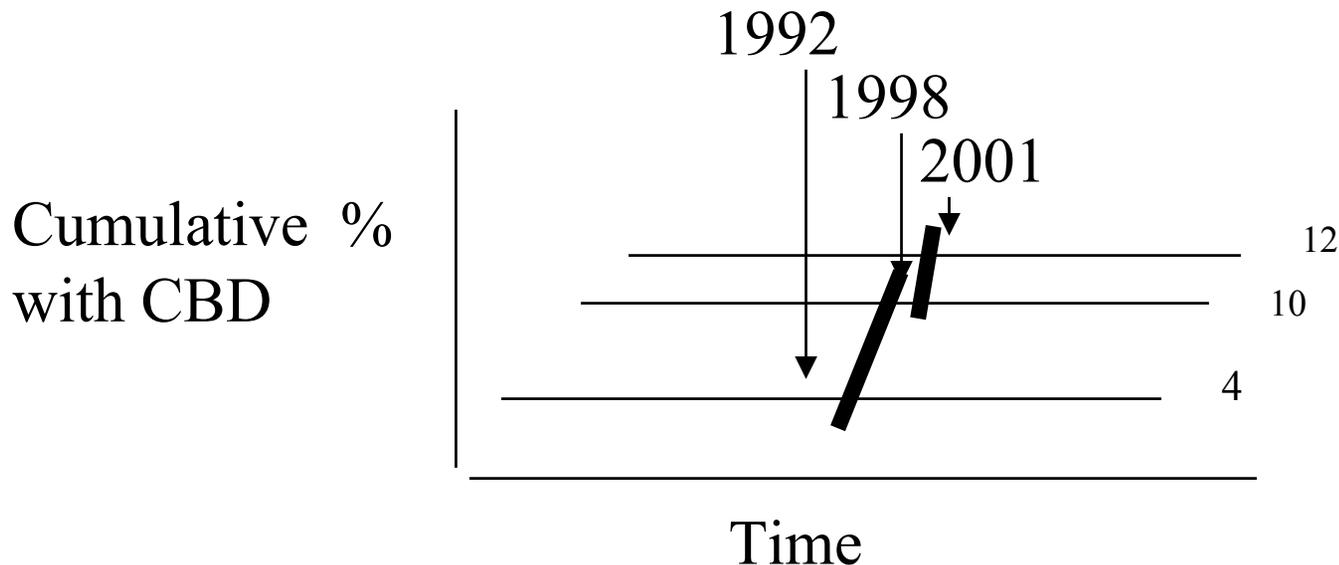
- Beryllium exposure:
 - With sufficient skin or lung exposure, all or almost all will have a primary immune response (become sensitized)
- Sensitization markers
 - “All” will develop a positive BePT
 - “Many” will develop a positive BeBLPT
 - In “most” the positive BeBLPT is transient
 - “Some” will have up-regulation of the response in a variety of patterns indicated by variably positive BeBLPTs over time

Sensitization markers and CBD

- Persons with positive BeBLPTs have a high probability of having typical inflammation in the lung
 - Exposure years 1, 2 ~ 15%
 - Exposure year 3 ~ 40%
 - Exposure year 4+ ~ 60% or more
- Some of these will develop significant, progressive clinical disease
- Clinical course of the rest in doubt

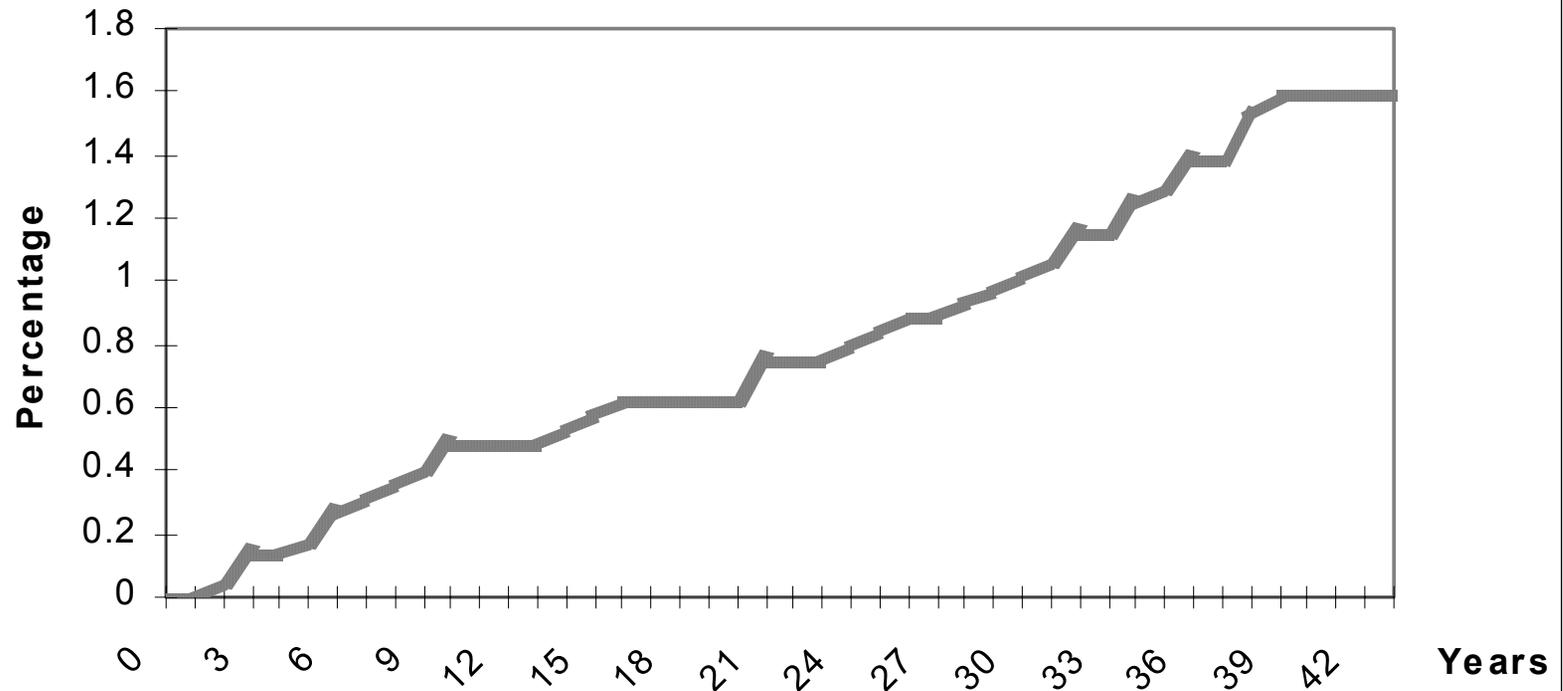
CBD enigma

- Through two surveys and ongoing testing, the cumulative % rises with time while the prevalence in each survey remains flat



Incidence of clinical CBD

⁵⁵⁻⁶⁴
**Cumulative Percentage of Employees Diagnosed with
Chronic Beryllium Disease from Year of Hire
Brush Wellman 1955-64 Hire Cohort**



Natural history of sub-clinical CBD

- Epidemiology suggests, as for the positive BeBLPT, that sub-clinical lung inflammation may be a temporary condition in some, in analogy to sarcoidosis
- “Sarcoidosis runs a variable course, with the disease resolving spontaneously in many patients.”
 - Srirling RG, Cullinan P, and Du Bois RM
“Sarcoidosis” in Interstitial lung Disease, 1998,
p.307

“What if all of the above were true?”

Interpretation of research

- CBD a 4 step process
 - 1) primary immune response (measure: BePT)
 - 2) immune activation (measure: BeBLPT)
 - 3) inflammation (measure: bronchoscopic biopsy)
 - 4) progressive fibrosis (measure: serious illness with fall in PFT, x-ray changes)

“If all of the above is true”

Interpretation of research

- Step 1 primary immune response, BePT: Only Curtis and Shima have adequately studied this. Shima showed clear general air level-response relationship
- Step 2 activation, BeBLPT: Current epidemiology studies this, but lack of a clear dose-response relationship suggests dose may not be the critical factor in activating the immune response

“If all of the above is true”

Interpretation of research

- Step 3 inflammation, biopsy: Current epidemiology shows closely linked to activation, except
 - Higher proportion inflammation/activation in BeO work?
 - Lag in proportion years 1, 2, 3
 - Dissociated in BWI mine and ore processing?
Due to no BeO exposure?
- Genetics of activation and inflammation appear similar

“If all of the above is true”

Interpretation of research

- Step 4 progressive fibrosis (serious illness)
Epidemiology not known
 - Numbers much smaller, diagnoses accumulate over long periods
 - Dissociated in BWI mine and ore processing.
Due to no BeO exposure?
- Genetics: Progressive fibrosis more closely associated with HLA DP1 Glu69?

“What if all of the above were true?”

Implications for research

- BeBLPT negative groups should not be labeled “not sensitized”
- There has to be clear delineation of the relationship of hypotheses to the different outcomes (sensitization, activation, inflammation or progressive fibrosis) and measures thereof
- Combining of outcome groups needs to be done and interpreted with exquisite care