PATHOGENESIS OF PNEUMOCONIOSES

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Development of disease

- **Host factors**

  individual susceptibility

- **Environmental factors**

  nature and duration of exposure, co-exposures

- **Particles**

  agent
  dimension
  surface morphology

  physical and chemical characteristics

Silica

- A chronic lung disease due to inhalation of crystalline silica (usualy quartz)
- Characterized by progressive parenchymal nodules and pulmonary fibrosis
- Silica or silicon dioxides is the most abundant mineral in the earth’s crust
- Occupations: Mining, quarrying, stonework, foundries, abrasive, ceramic industries

Silica

- **Cumulative dose**

  respirable dust/particle concentration

  crystalline silica content

  duration of exposure

Silica - Dose

- Quantity of material
  - Concentration in the air
    by mass: mg/m^3
  - Duration of exposure
    hours, days, years
  - Cumulative exposure
    (concentration x duration)

Silica

- Lymph node silicosis precedes lung silicosis?
  - Lymph node-only associated with lower exposures than lung silicosis

    Cox-Ganser JM et al. J Occup Environ Med 2009
  - As cumulative exposure to silica increased, lung silicosis increased at the expense of lymph node-only silicosis and non silicosis

    Taeger D et al. Arch Environ Occup Health 2011

Silica

- Fibrogenic particles
  - Trydimite > cristobalite > quartz (recently cut)
- Less (non) fibrogenic particles
  - Amorphous silica

Silica

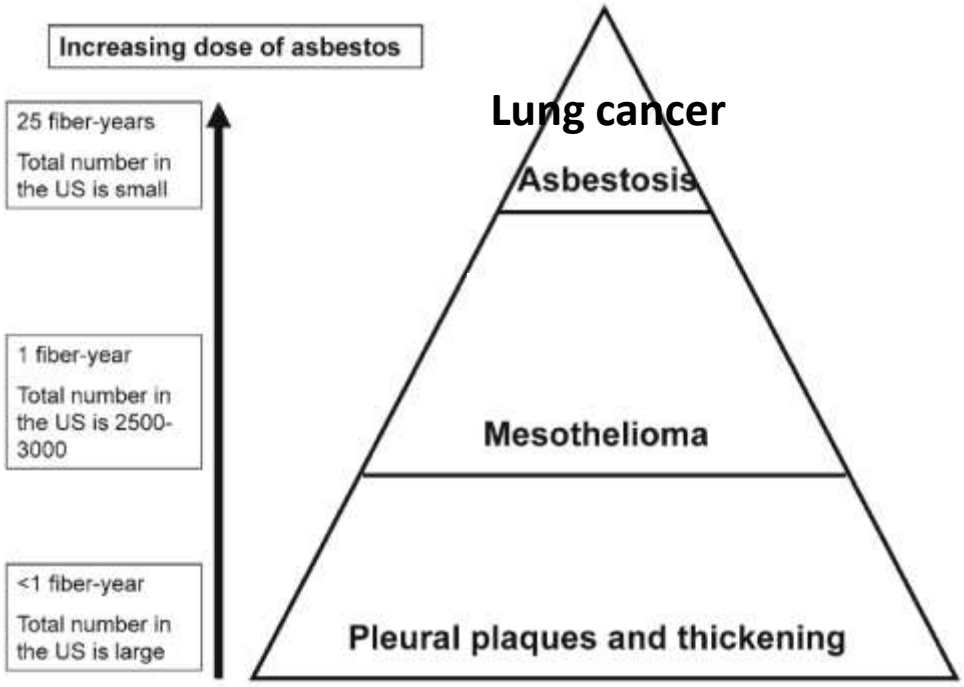
- In 1997 the International Agency for Research on Cancer (IARC) classified crystalline silica inhaled in the form of quartz or cristobalite from occupational sources as a human (Group I) Carcinogen… (reinforced in 2009)

Asbestos

- Amphibole hypothesis: Amphiboles, especially crocidolite, are more fibrogenic and carcinogenic than chrysolite (?)
- Dose response: years of exposure, intensity, dust control measures (masks)
- Latency period: 10-40 years typically
  - < 5 years after initial exposure unlikely due to asbestos
- Genetic susceptibility (not fully understood)
  - Anti-oxidant defenses
  - Inflammatory/immune response
  - Gene polymorphisms (GSTM1, SOD2, α 1AT, XRCC1/3)
  - p53

Asbestos

- Dependance on the magnitude of fiber exposure



A Clinical Guide to Occupational and Environmental Lung Diseases
Yuh-Chin Huang, Andrew Ghio, Lisa Maier Eds. Springer 2012

Mesothelioma Biomarkers

- Mesothelin-related peptides (SMRP)
  - Approved by FDA in 2007 for monitoring the course of mesothelioma with epithelioid features
  - Not approved for diagnosis
  - Meta-analysis: at a threshold level with 95% specificity, serum mesothelin had a sensitivity of 32%

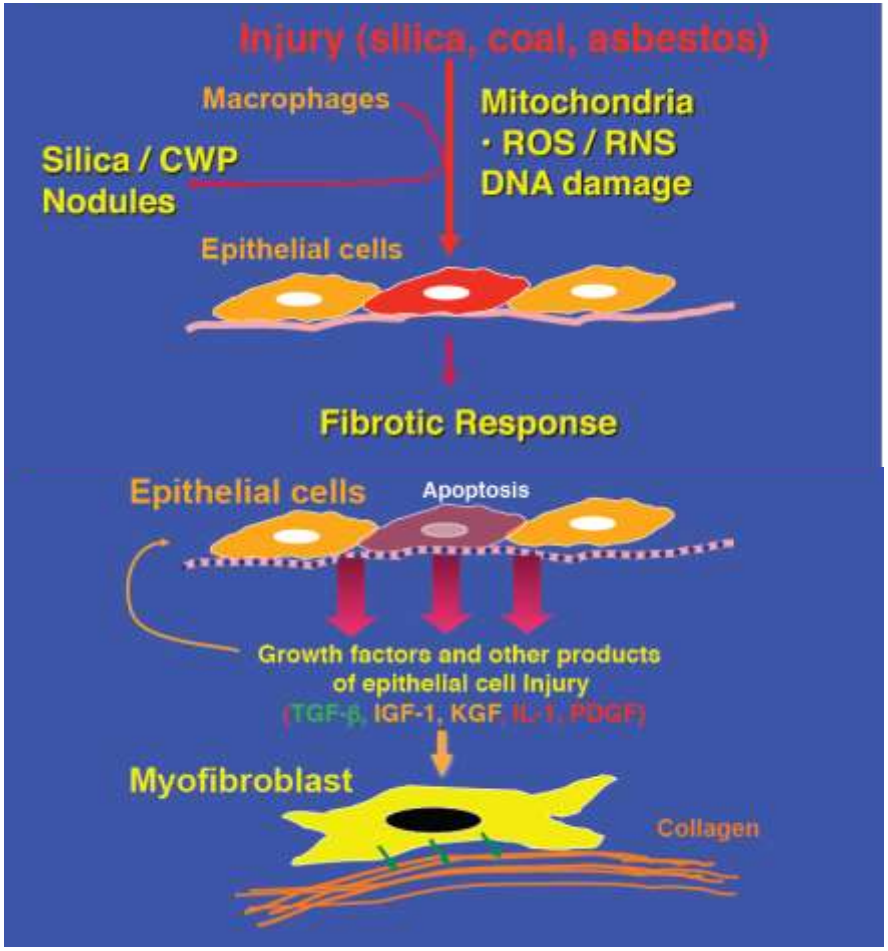
Hollevoet K et al. J Clin Oncol 2012

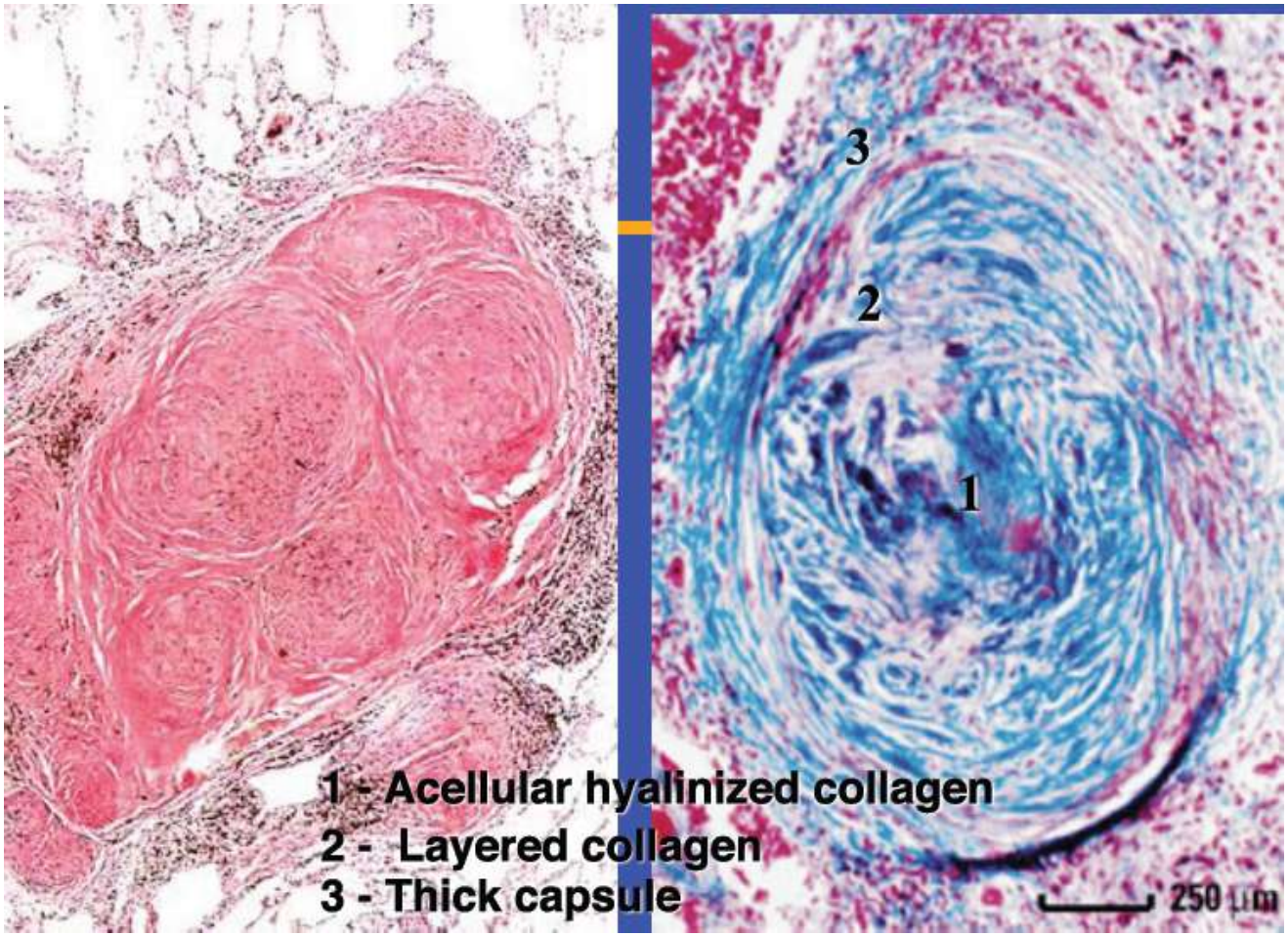
- Osteopontin
  - Plasma osteopontine has better performance characteristics than serum ostepontin

$\rightarrow$ Combining serum mesothelin and plasma osteopontin did not improve diagnostic performance

Creaney J et al. Lung Cancer 2011

Pathogenesis




3
2
1
1 - Acellular hyalinized collagen
2 - Layered collagen
3 - Thick capsule
250 µm

Rare Interstitial Lung Diseases of Environmental origin

C Robalo Cordeiro, TM Alfaro, S Freitas, J Cemlyn-Jones, AJ Ferreira

Table 1. Pathological abnormalities and related exposures

Pathological patterns	Related exposures
Usual interstitial pneumonia	Asbestos and other fibrous silicates, wood and metal dusts, mixed dust, mica, uranium mining, plutonium, kaolin, rare earths, cobalt and aluminium
Nonspecific interstitial pneumonia	Organic antigens and reactive chemicals
Desquamative interstitial pneumonia	Textile work, cobalt, aluminium, plutonium, asbestos and talc
Respiratory bronchiolitis-interstitial lung disease	Second-hand smoke
Organising pneumonia	Spray painting textiles (acramin) and nitrogen oxide species
Diffuse alveolar damage	Irritant inhalational injury: nitric oxide, sulfur oxygen species, cadmium, beryllium, chlorine, acid mists and waterproofing materials
Giant cell interstitial pneumonia	Cobalt
Pulmonary alveolar proteinosis	High-level exposure to silica, titanium or aluminium dust
Constrictive bronchiolitis	Diacetyl, fibreglass coating materials, nitric oxide, sulfur oxygen species and chlorine gas
Granulomatous inflammation (sarcoid or sarcoid-like)	Beryllium, organic antigens, zirconium, aluminium, titanium and mixed dust

Adapted from [1] and [2].

Eur Respir Mon 2011, 54: 301-316

Silicosis

Chi Chiu Leung, Ignatius Tak Sun Yu, Weihong Chen

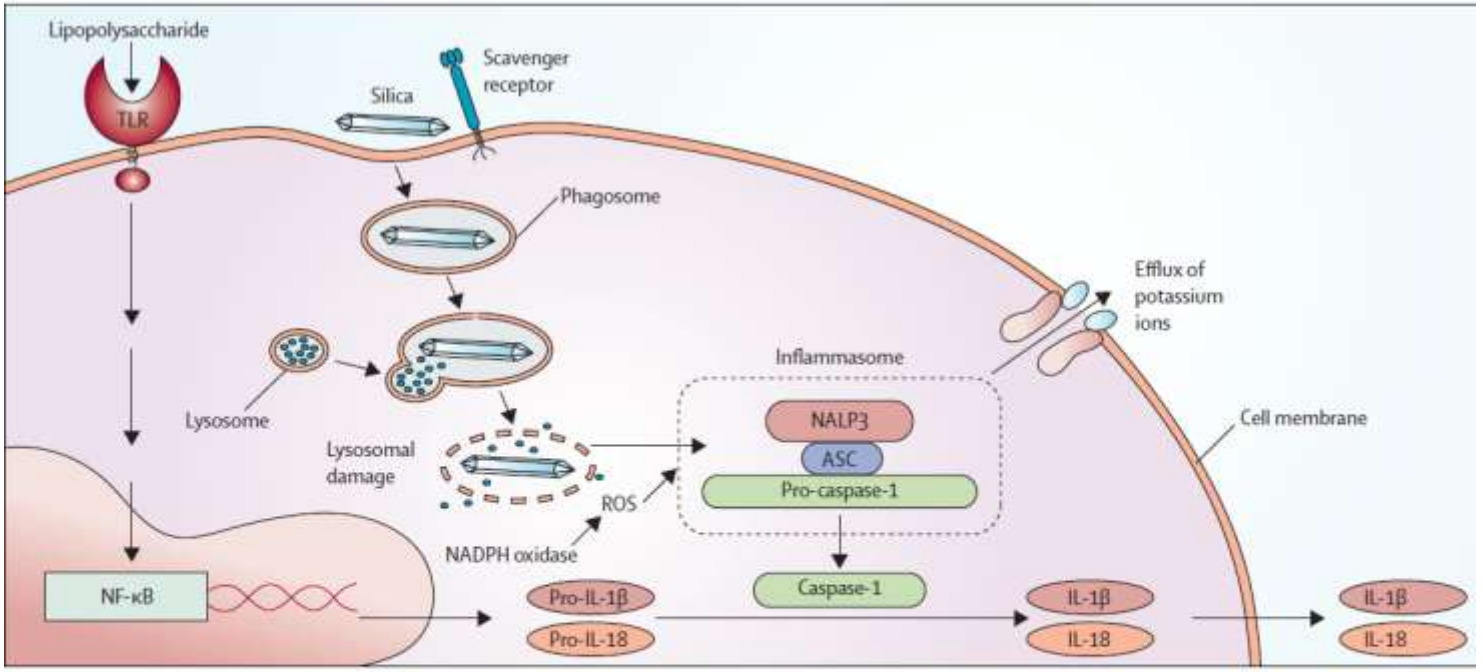
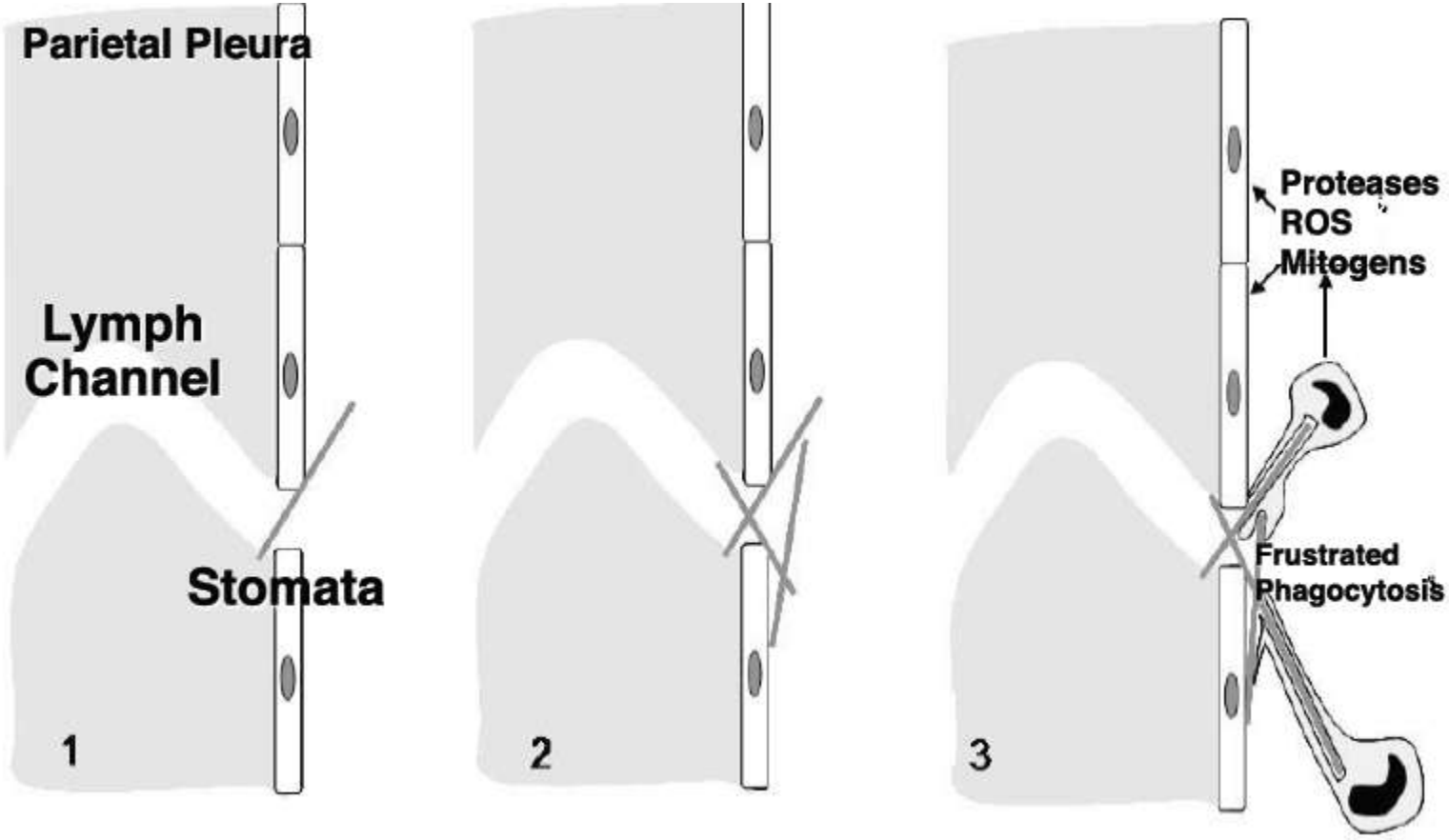


Figure 2: **Activation of the NALP3 inflammasome by a silica crystal after initial priming by a lipopolysaccharide**
Phagocytosis of crystalline silica leads to active swelling of phagosomes, followed by phagosomal destabilisation, releasing their contents into the cytosolic compartment.[59] Activation of the nucleotide-binding domain, leucine-rich repeat protein NALP3 leads to its association with the intracellular adapter protein ASC, which combines with and activates pro-caspase-1. The resulting active enzyme complex (NALP3 inflammasome) activates the potent proinflammatory molecules suc as IL-1β and IL-18. Activation of the NALP3 inflammasome by silica also necessitates generation of ROS by an NADPH oxidase after particle phagocytosis and an efflu of intracellular potassium ions, suggesting a possible interaction of the silica with a membrane-associated protein.[62,68] TLRs or IL-1 receptors do not seem to be essenti for activation of the inflammasome.[67,69] However, secretion of IL-1β by mouse or human macrophages in response to silica or asbestos in vitro seems to be a two-step process because priming by a lipopolysaccharide is necessary.[67,69] Scavenger receptors seem to have a role in the recognition and uptake of silica. TLR=toll-like receptor ROS=reactive oxygen species. ASC=apoptosis-associated speck-like protein containing a caspase recruitment domain. NF-κB=nuclear factor-κB. IL=interleukin.

Lancet 2012; 379: 2008–18

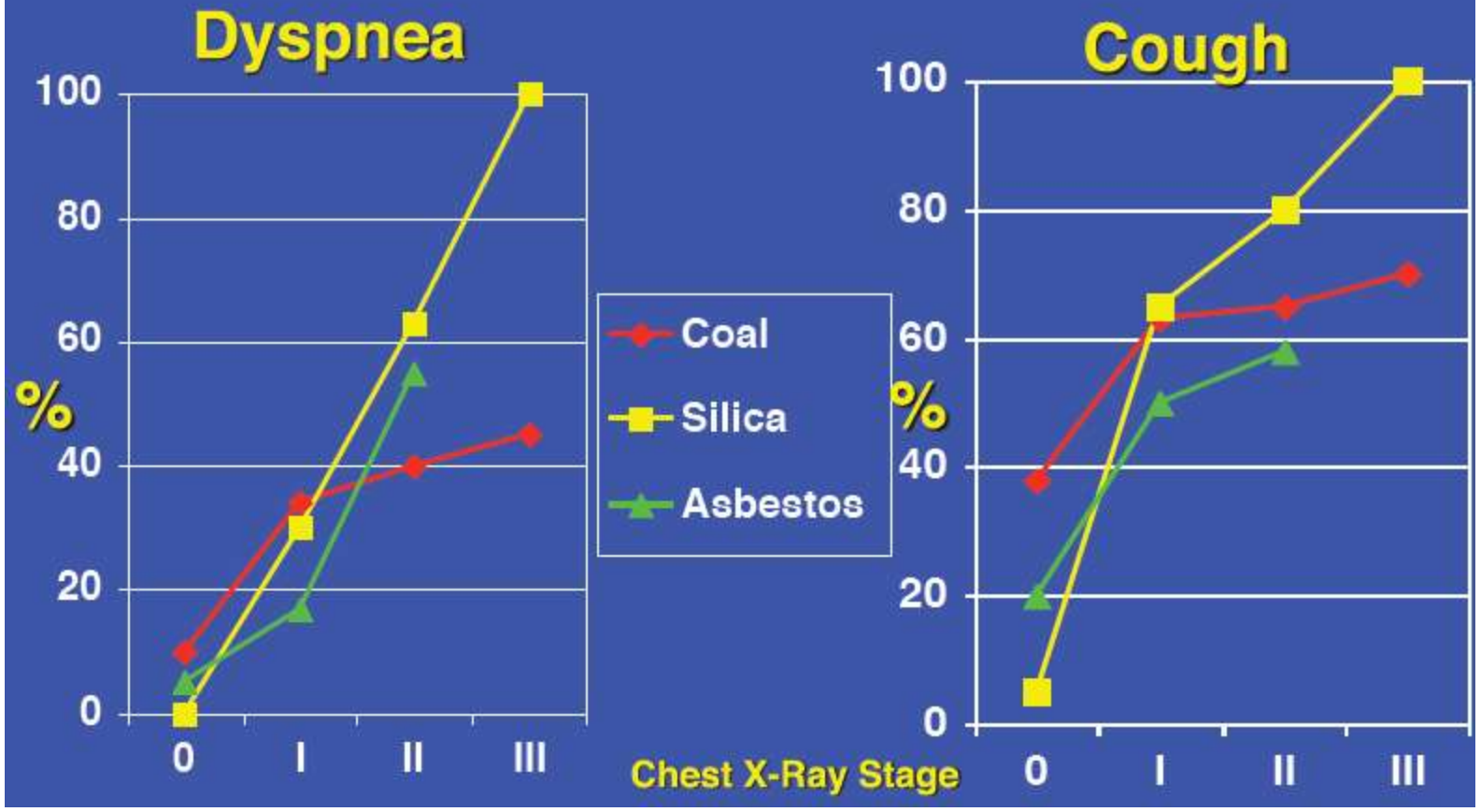
Long fiber retention in the parietal pleura

Donaldson K et al. Particle and Fiber Toxicology 2010



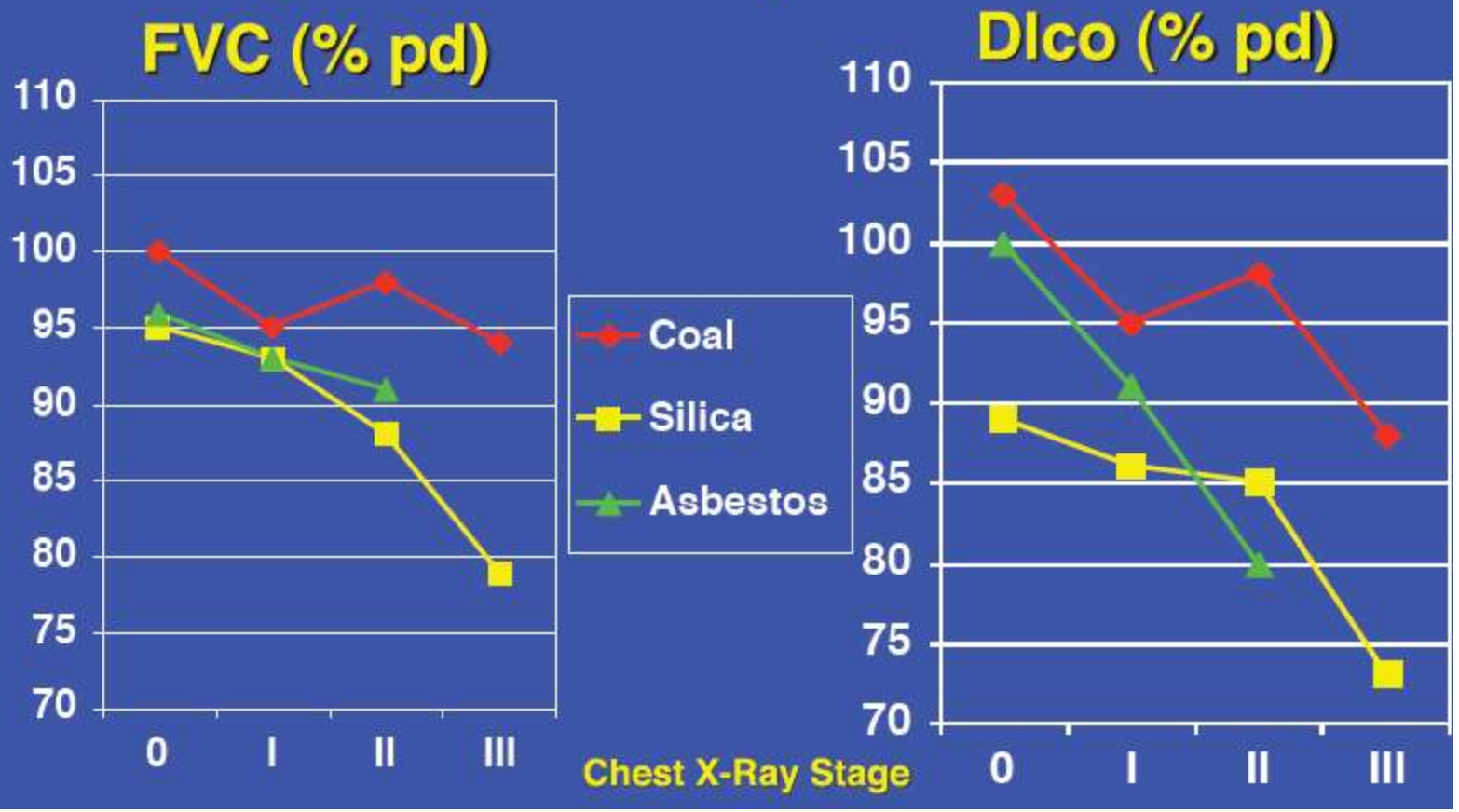
Silica (n = 220), Coal (n = 511) and Asbestos (n = 277) Workers: CXR

Wang & Christiani *J Occup Med* 2000; 42:1076



Silica, Coal and Asbestos Workers: PFT v. CXR

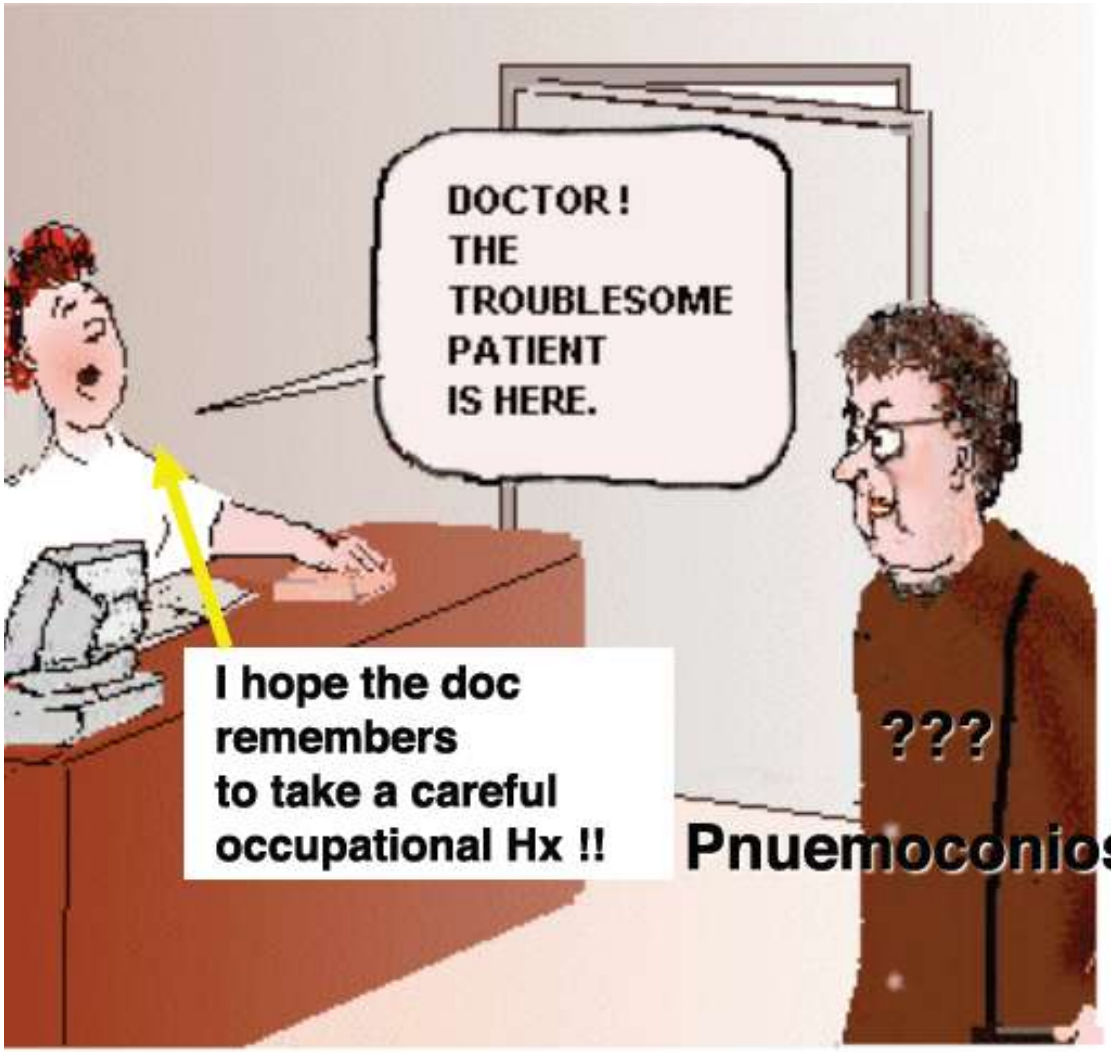
Wang & Christiani *J Occup Med* 2000; 42:1076



Timely intervention strategies!

A through understanding of these mechanisms may enable the identification of prediction markers and early detection of Pneumoconiosis

- Biomarkers of exposure, effect and susceptibility
  Silicosis and CWP: Clara cell protein-16, TNF-α IL-8, ROS, PDGF, …
- Exhaled Breath Condensate
  8-isoprostanes, H2O2, PGE2, Glutathione, LTs, Ils, Nitrates, pH,…
- Genetic variability and genetic/environmental interaction
  Silicosis and CWP: TNF-α polymorphisms


DOCTOR!
THE
TROUBLESOME
PATIENT
IS HERE.
I hope the doc
remembers
to take a careful
occupational Hx !!
???
Pnuemoconiosis
Quack