

WORK-RELATED INTERSTITIAL LUNG DISEASE: BEYOND PNEUMOCONIOSIS

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DISCLOSURES

**I HAVE NOTHING TO
DISCLOSE**

SUPPORTING MATERIALS

- talk available online

*[http://carlreynolds.net/work-related-
ild-talk-sanfran-march-2017/](http://carlreynolds.net/work-related-ild-talk-sanfran-march-2017/)*

- additional material available

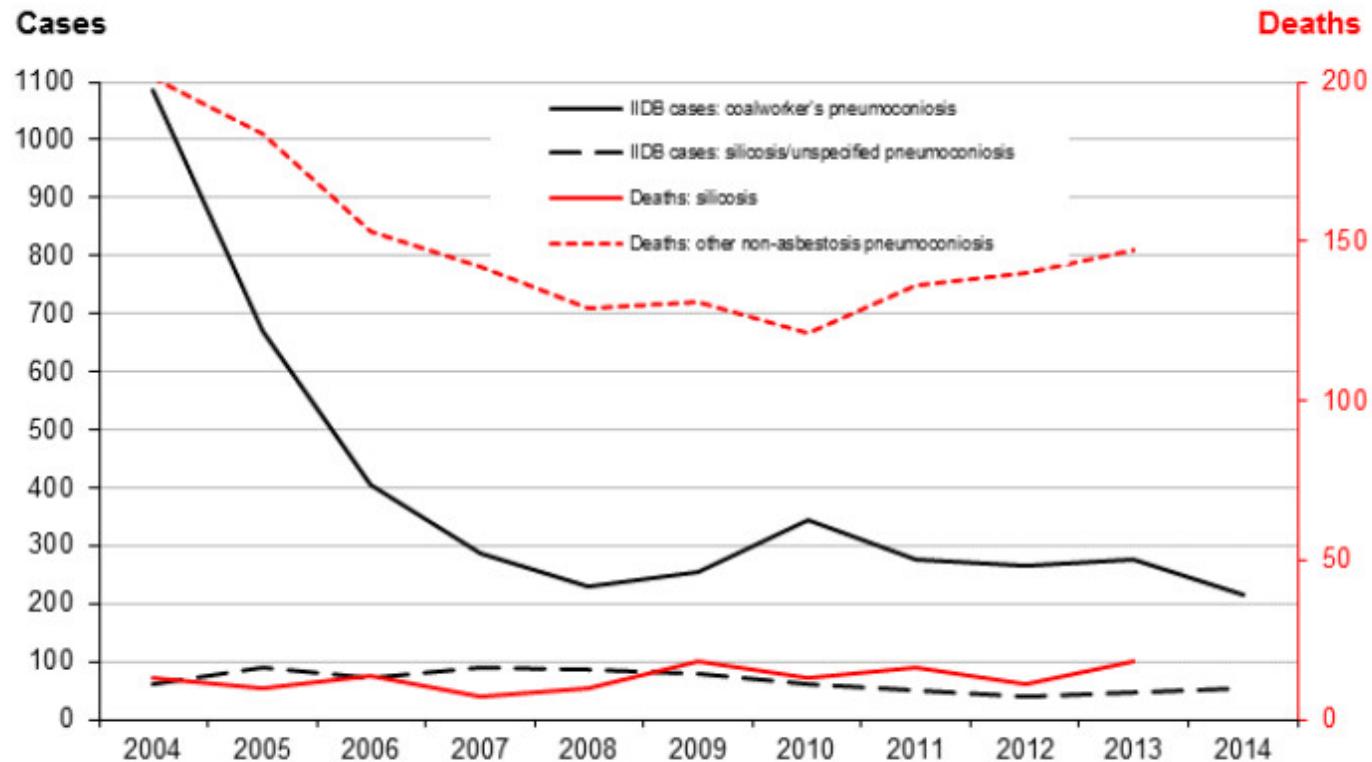
*[https://github.com/drcjar/work-related-
ild-talk-sanfran-march-2017](https://github.com/drcjar/work-related-ild-talk-sanfran-march-2017)*

BEYOND PNEUMOCONIOSIS?

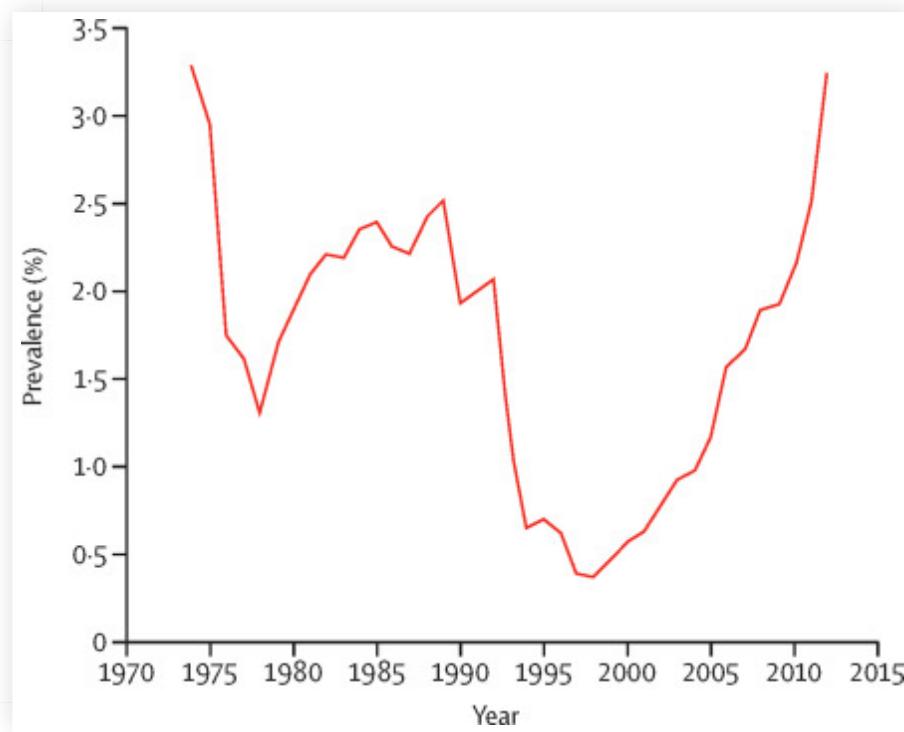


Kellingley colliery workers

Figure 1: Pneumoconiosis (excluding asbestosis) in Great Britain, 2004-2014



HSE Pneumoconiosis figures



Prevalence of progressive massive fibrosis in underground coal miners with 25 years of more exposure in three states of the USA (1)

**WHAT IS
WORK-RELATED ILD?**

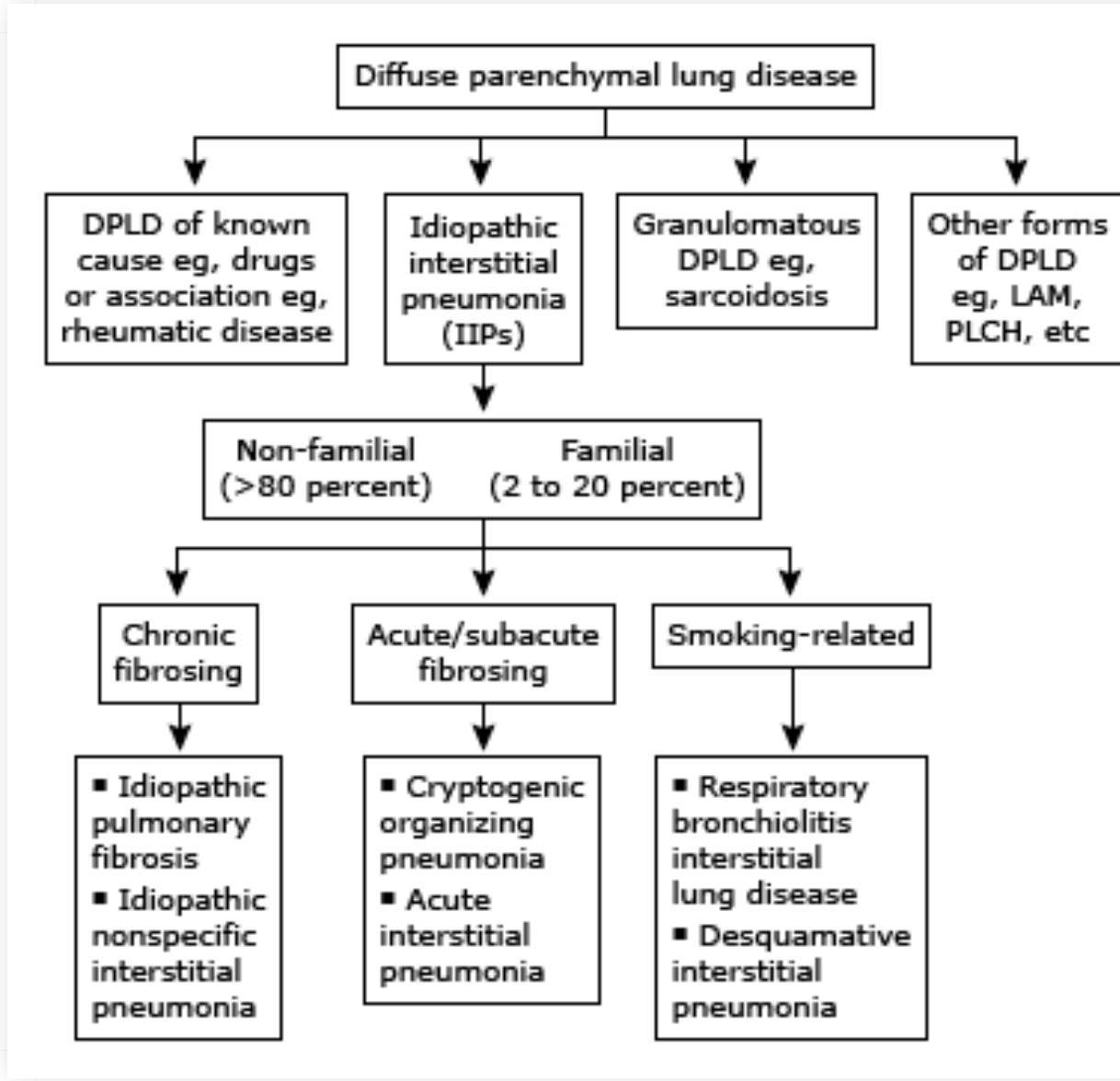
DEFINITIONS

**WORK-RELATED
DOESN'T MEAN
OCCUPATIONAL**

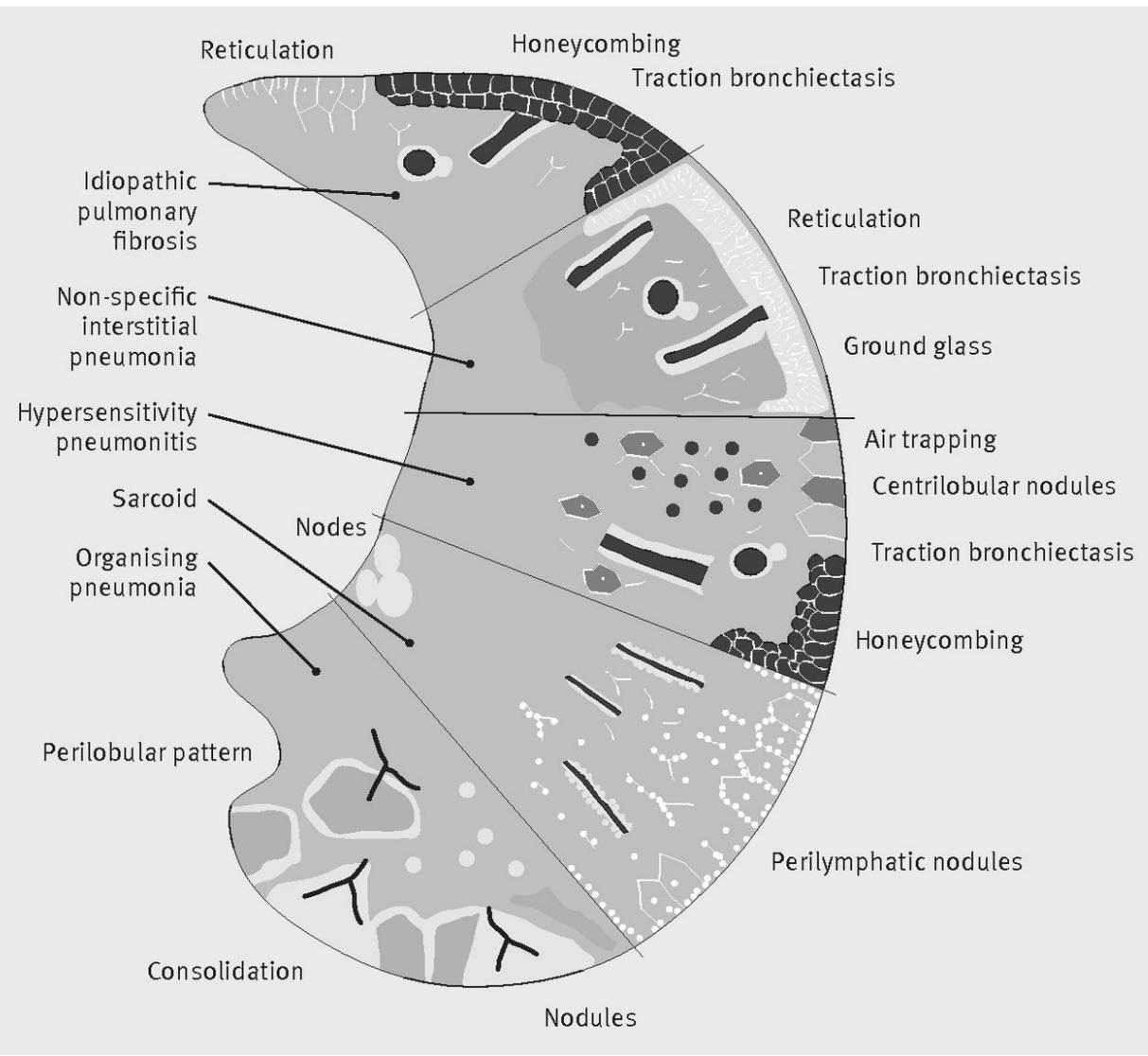
- occupational diseases are primarily caused by exposure to risk factors arising from work
- work-related diseases have multiple causes; factors in workplace may play a role (WHO 2017)

**DIFFUSE
PARENCHYMAL LUNG
DISEASE IS CONFUSING**

- ILD or DPLD
- heterogeneous group of disorders characterised by inflammation and fibrosis of the interstitium
- interstitium refers to tissue between the pulmonary alveoli and the bloodstream
- in practice disease can also involve airway



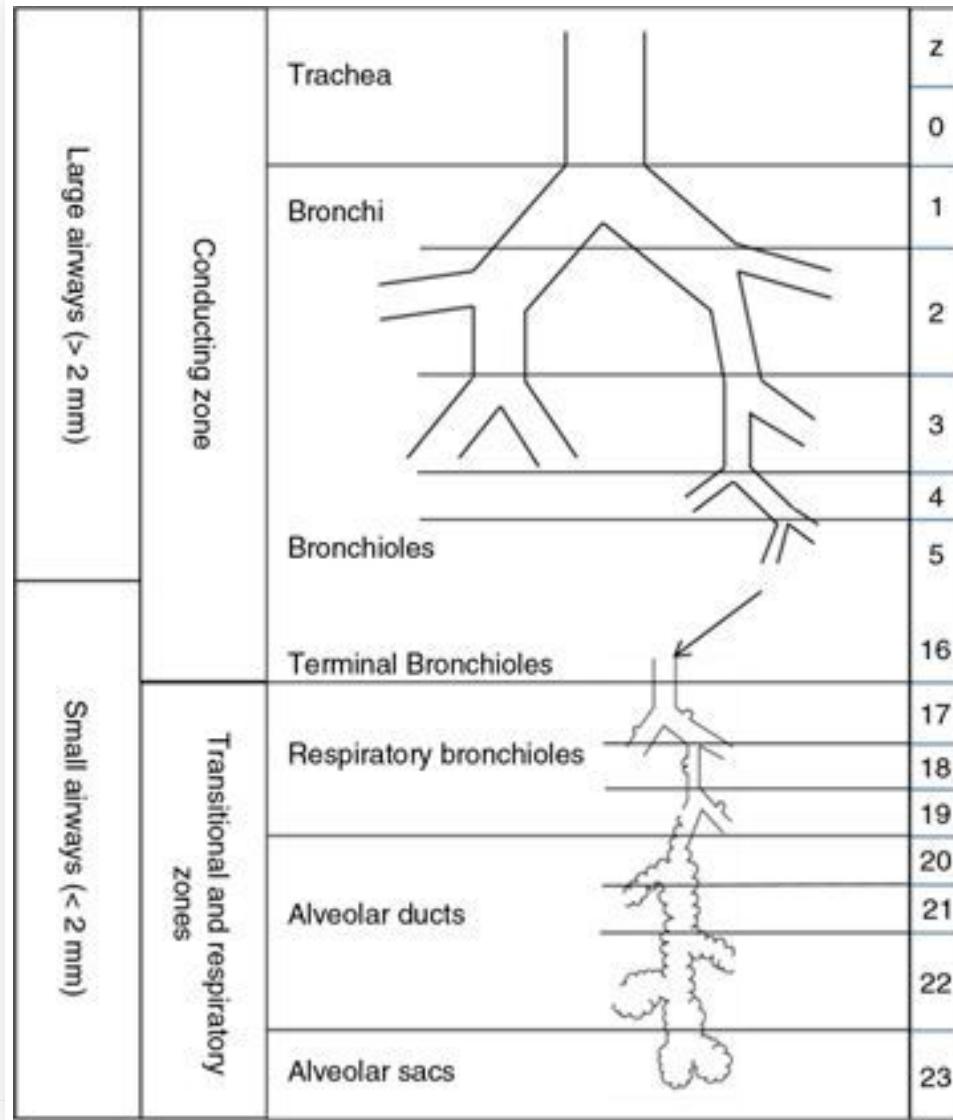
An ILD Taxonomy (7)



CT appearance ILD (5)

LUNG PHYSIOLOGY AND INTERSTITIAL EXPOSURES

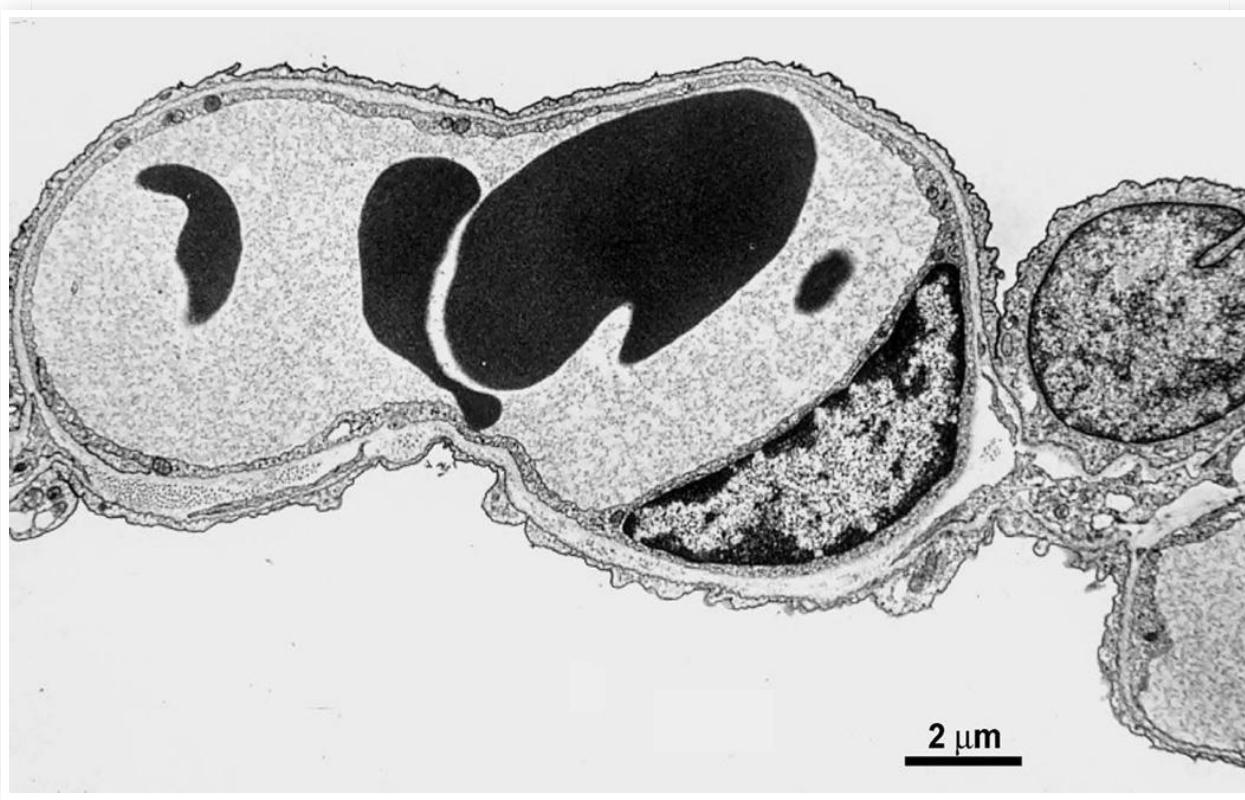
- Diffusion of gases across blood-gas barrier is passive and governed by Fick's Law.



Weibel model

*V_{gas} (diffusing) is proportional to
Area/Thickness * D(diffusion constant) *
(P₁ - P₂)*

D = solubility / root of the molecular weight of the gas



2 μm

Blood gas barrier

- $2\mu\text{m}$ across (for ref sheet of paper is $50\mu\text{m}$, $1/20$ th of a mm or 0.05mm).
- $25\times$ thinner than that. 300 million alveolii.
- Each alveoli is 0.0042mm^3 (a grain of sand is 0.06mm^3 , so an alveoli is about 14 times smaller).
- Surface area of a tennis court.

*TV 500ml, dead space 150ml, RR 15/min,
350ml*15 = approx 5L/min -> 7200L/day*

**AMPLE OPPORTUNITY
FOR SUFFICIENTLY
SMALL PARTICLES TO
MEET THE
INTERSTITIUM**

WORK-RELATED ILD

**ILD INCIDENCE
30/100,000 PER YEAR
AND PREVALENCE
70/100,000
(APPROXIMATELY)**

- precise population prevalence and incidence of ILD hard to establish (classification problems, limitations of registry and insurance claim data).
- best historic estimate of incidence 30/100,000 per year, prevalence 70/100,000. (10)
- IIP most common, IPF 1/3rd of cases, more common in men.

**15-20% OF ILD DUE TO
OCCUPATIONAL AND
ENVIRONMENTAL
EXPOSURES**

**AETIOLOGIES ARE
MANY**

- common: include organic antigen, isocyanates, silica, cadmium, diacetyl, asbestos
- less common: cobalt, rare earths, plutonium

**RELATIONSHIP
BETWEEN AETIOLOGIC
AGENT AND
PATHOLOGICAL
PATTERN OFTEN NOT 1:1**

Pathology	Common Causative Exposures	Rare Causative Exposure
Granulomatous pulmonary inflammation	Hypersensitivity pneumonitis (organic antigen, isocyanates, pyrethrum, anhydrides), beryllium	Cobalt, aluminum, titanium, zirconium, talc
Usual interstitial pneumonia (UIP)	Asbestos, mixed dust, agents that cause hypersensitivity pneumonitis	Cobalt, wollastonite, attapulgite, sepiolite, mica, kaolin, rare earths, aluminum
Desquamative interstitial pneumonia (DIP)	No common exposures	Cobalt, aluminum, plutonium, asbestos, talc
Nonspecific interstitial pneumonia (NSIP)	Hypersensitivity pneumonitis (organic antigen, isocyanates, pyrethrum, anhydrides)	Coal and silica can rarely cause a diffuse interstitial fibrosis similar to fibrotic NSIP
Organizing pneumonia	NOx (silo-filler's lung)	Spray painting textiles—Acramin FWR.
Acute interstitial pneumonia (AIP) (pathology = diffuse alveolar damage)	Irritant inhalational injury—NOx, SOx, cadmium, beryllium, chlorine, acid mists, etc.	
Giant cell interstitial pneumonia (GIP)	Cobalt	
Pulmonary alveolar proteinosis	No common exposures	High level exposure to silica, titanium, or aluminum dust
Constrictive bronchiolitis	Flavoring workers (diacetyl), NOx, SOx, chlorine gas	

NOx indicates nitrogen oxide species; SOx, sulfur oxide species.

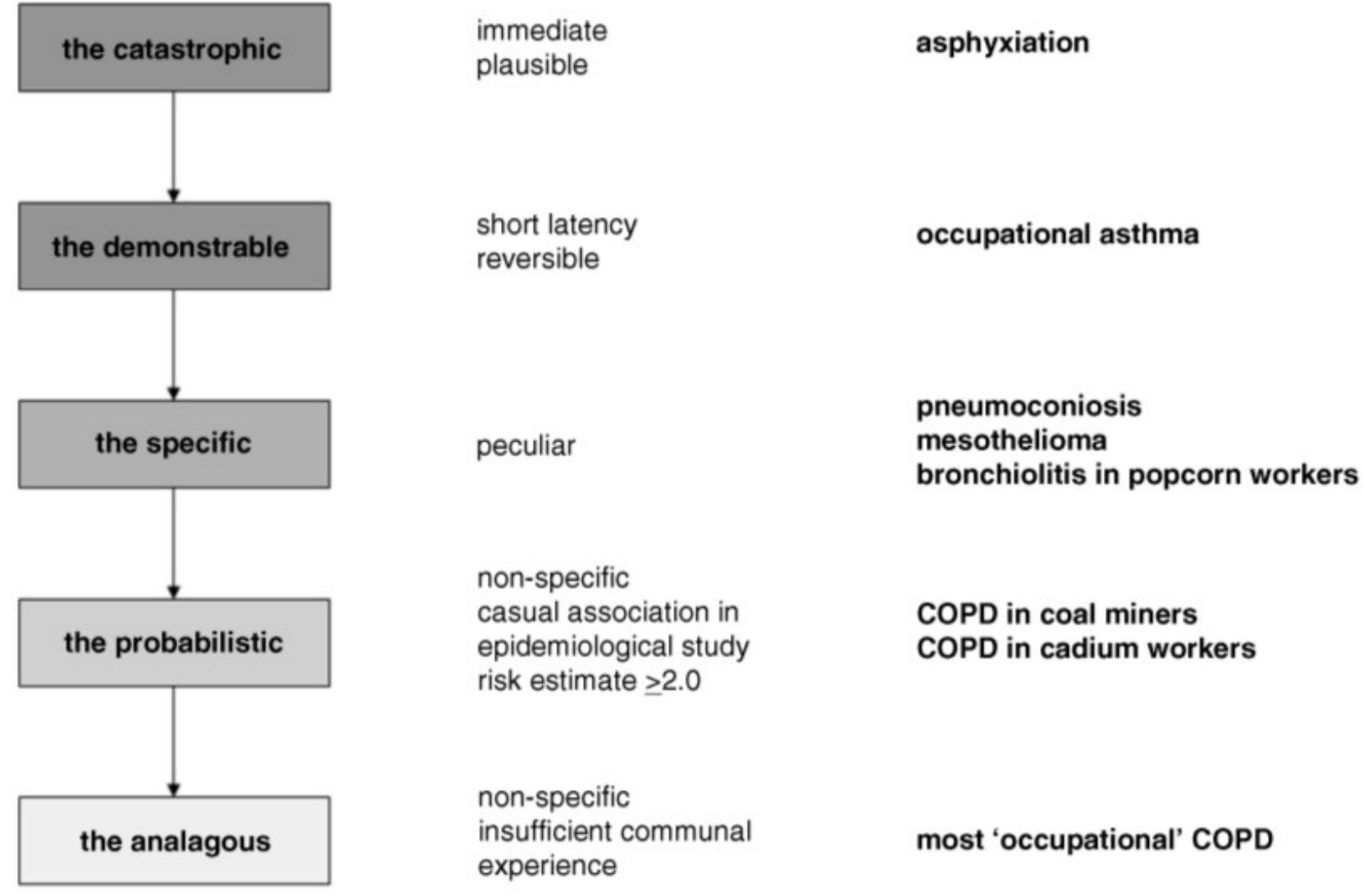
Pathologic Patterns and Causes (4)

CLINICAL FEATURES

- Respiratory symptoms with an appropriate occupational or environmental exposure history
- Host-factor (e.g adaptive immune response, systemic) vs exposure factor dominant presentations (local inflammatory response)
- Investigations

**ATTRIBUTION
FREQUENTLY
NON-TRIVIAL**

**NEW WORKPLACE AND
ENVIRONMENTAL
EXPOSURES ALL THE
TIME**



A hierarchy of attribution in occupational lung diseases (11)

RECENT OUTBREAKS

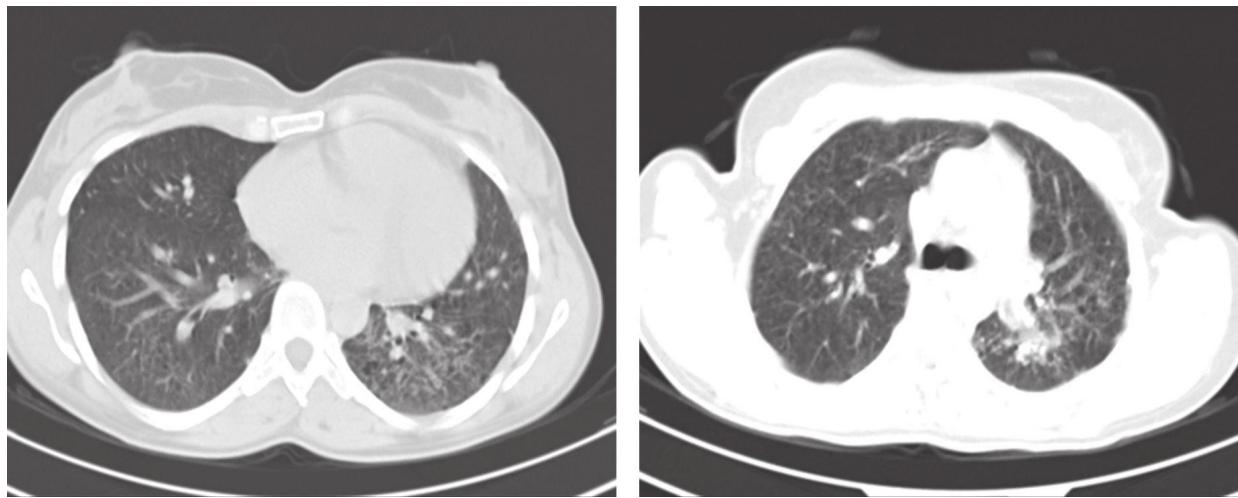
I'LL COVER THREE
DISEASES WHERE THE
HARD WORK OF
ATTRIBUTION HAS
ALREADY BEEN DONE

1. Ardystil
2. Indium tin oxide
3. South Korean lung

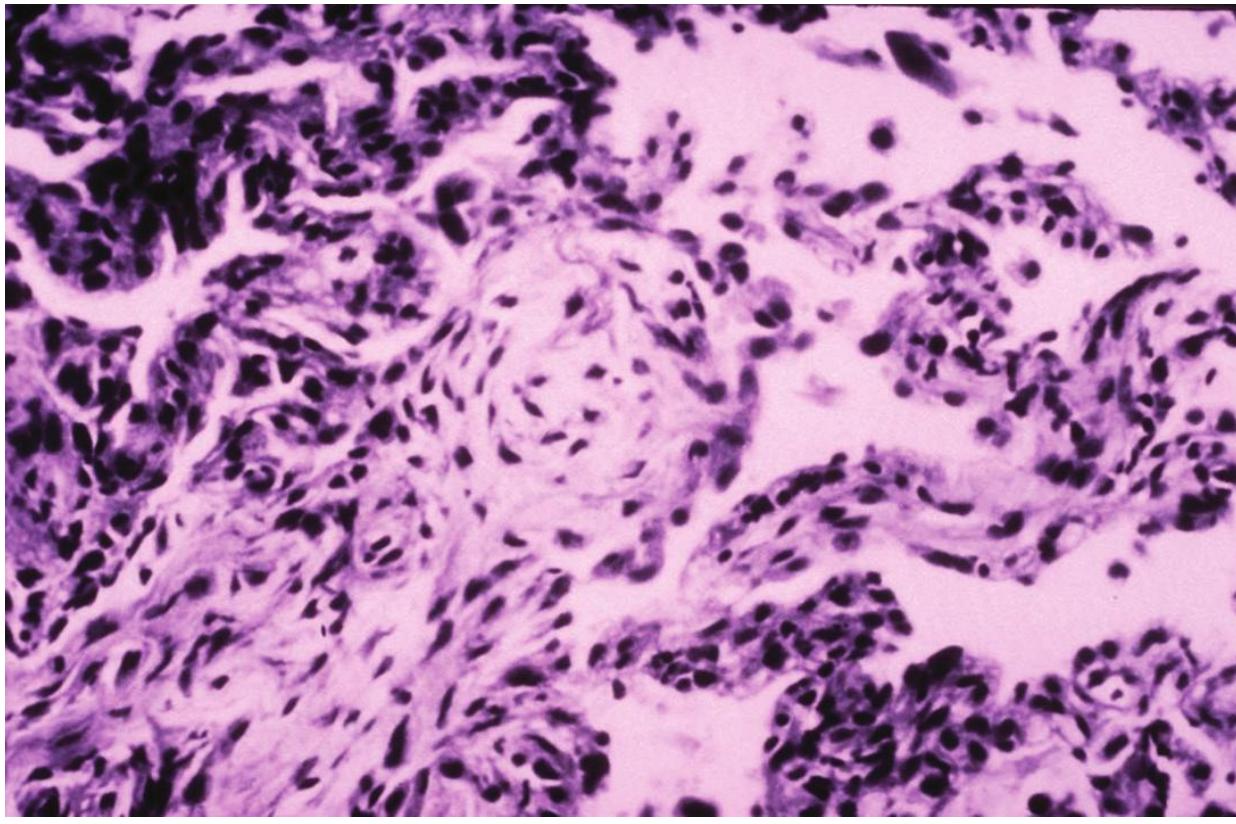
ARDYSTIL

- April 1992, two young women who worked at a textile factory were treated for interstitial lung disease and severe pulmonary insufficiency in Valencia.
- Prompted investigation of all textile factories (A-H) using same spraying technique in the area
- 257 employees identified. 22 cases who met radiological and biopsy criteria for organising pneumonia. Six fatal cases.

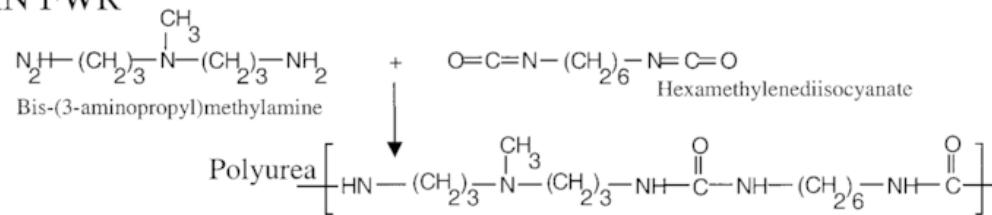
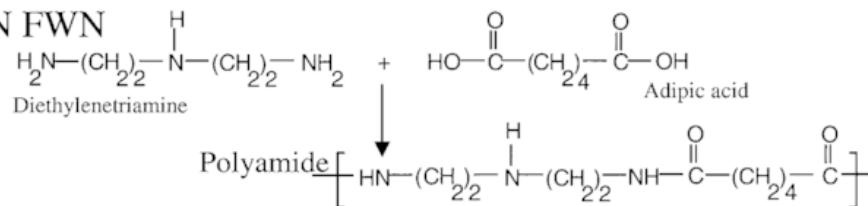
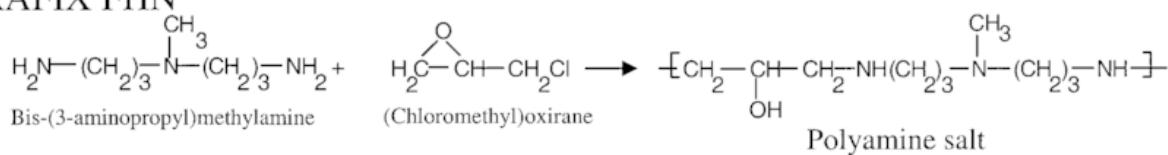
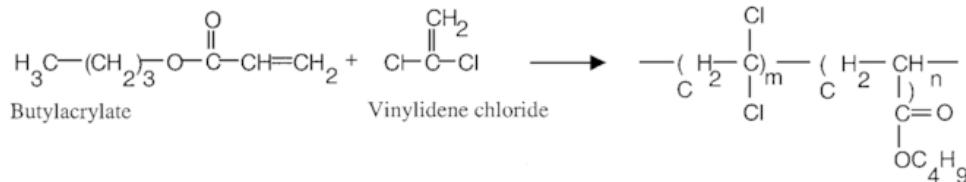
- Factory A had the highest risk of being a case (RR=24.3; 95% CI=5.7-104.4), followed by Factory B (RR=11, 95% CI=11.9- 62.9) and only two out of 22 cases had never worked in factories A or B.
- It was found that only in factories A and B had the presence of an airborne chemical by the trade name Acramin FWR that recently been substituted with another related compound Acramin FWN.
- Subsequently a similar outbreak occurred in Algeria.



Chest computed tomography image of Acramin (Ardystil) dye-associated organising pneumonia. Two patients with dyspnoea, reduced FEV1 and FVC. 2005. (1)



Cryptogenic organising pneumonia pattern in a lung biopsy
of an Acramin (Ardystil) dye-exposed worker. (1)

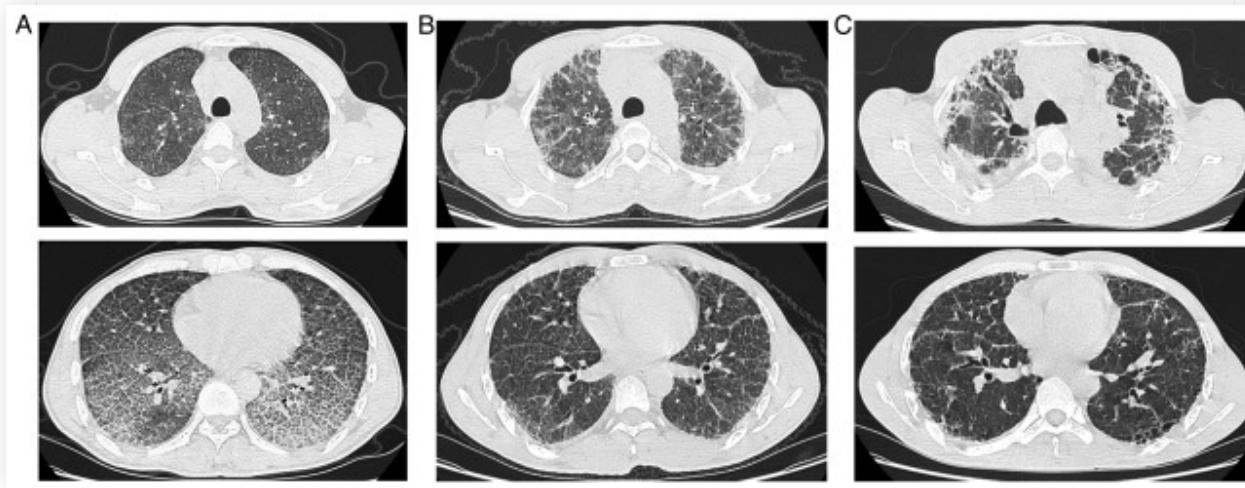
ACRAMIN FWR**ACRAMIN FWN****ACRAFIX FHN****ACRAMOLL W**

Chemical structure of Acramin FWN and Acramin FWR (12)

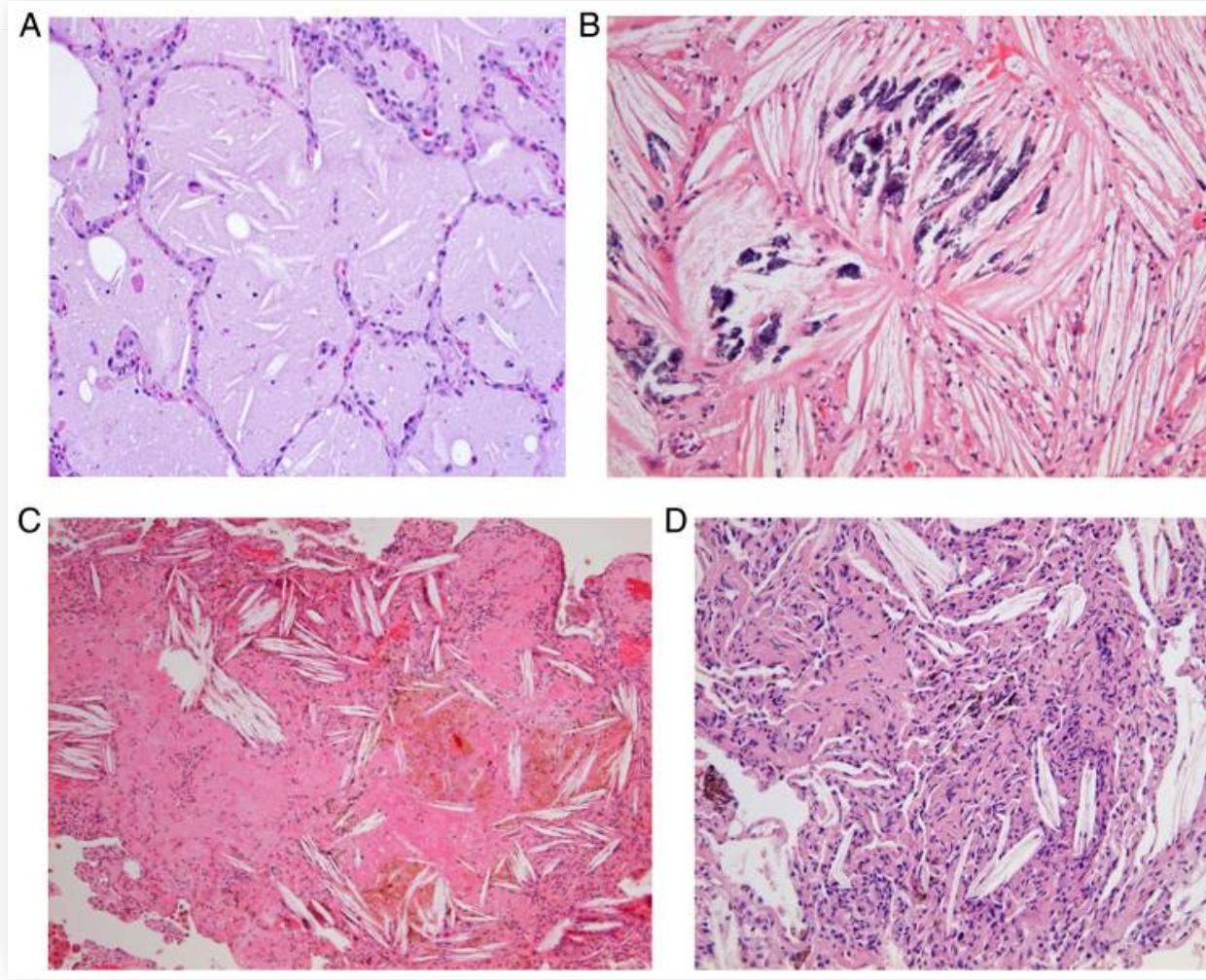
- Acramin FWR (tradname Ardystil) recently introduced as a replacement for Acramin FWN at the two factories where majority of cases had worked.
- Animal studies confirmed respiratory toxicity.
- Thought that highly negatively charged long-chain molecular structure of Acramin FWN contributes causes toxicity.

INDIUM TIN OXIDE

- Indium tin oxide (ITO) is a sintered material used in making crystal displays for televisions and computers.
- First case of ITO-associated interstitial pneumonitis was reported in 2003 in a 27-year-old Japanese worker (1)
- Cases in Japan, US, and China confirm interstitial pneumonia similar to UIP, emphysema, PAP in indium workers. Two patients have died to date. (13)
- Like Ardstyl outbreak notable that cases are young, have severe respiratory disease, and colleagues who are also unwell.



CT showing progression of disease over three years in a 28 year-old Indium worker. Ground glass opacities and interlobular thickening. (13)



Range of histopathological features. A-C features of alveolar proteinosis. D multinucleated giant cells, interstitial fibrosis, and brown particles composed predominantly of indium.
(13)

SOUTH KOREAN LUNG



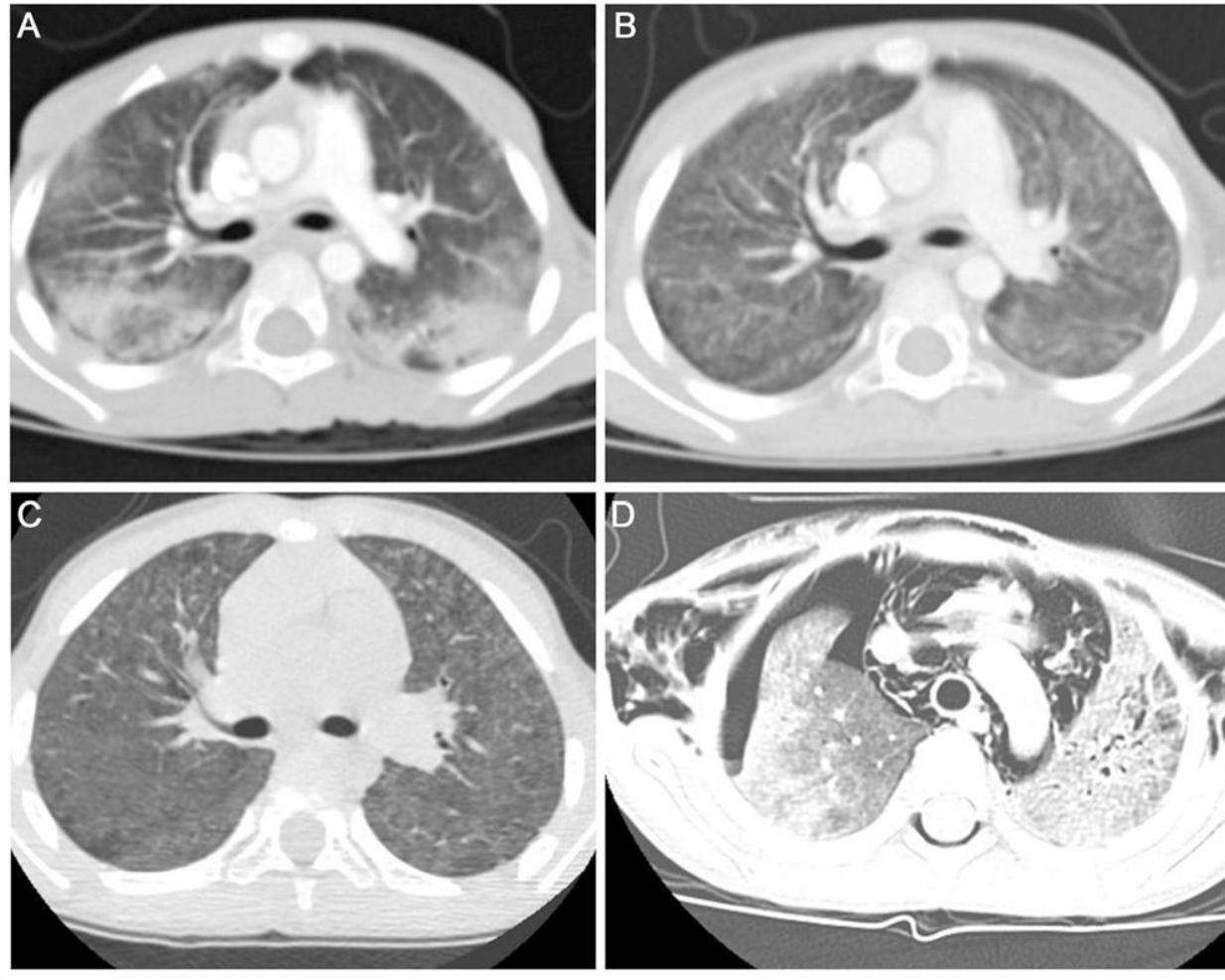
"A former South Korean executive of UK-based Reckitt Benckiser has received a seven-year prison sentence over a humidifier disinfectant linked to the death of around 100 people". BBC News website (accessed Jan 17 2017)

- Household clustering was observed in a series of patients admitted to ICU with severe respiratory distress in the spring of 2011. (15)
- Case series consisted of 17 patients (15 of which were female) with median age 35. Six were pregnant at presentation.
- All presented with cough and dyspnoea. CT showed patchy consolidation followed by ground glass opacity and bronchiolocentric fibrotic changes.
- Ten patients required mechanical ventilation. Four had lung transplants. Five of the six who did not have a lung transplant died.

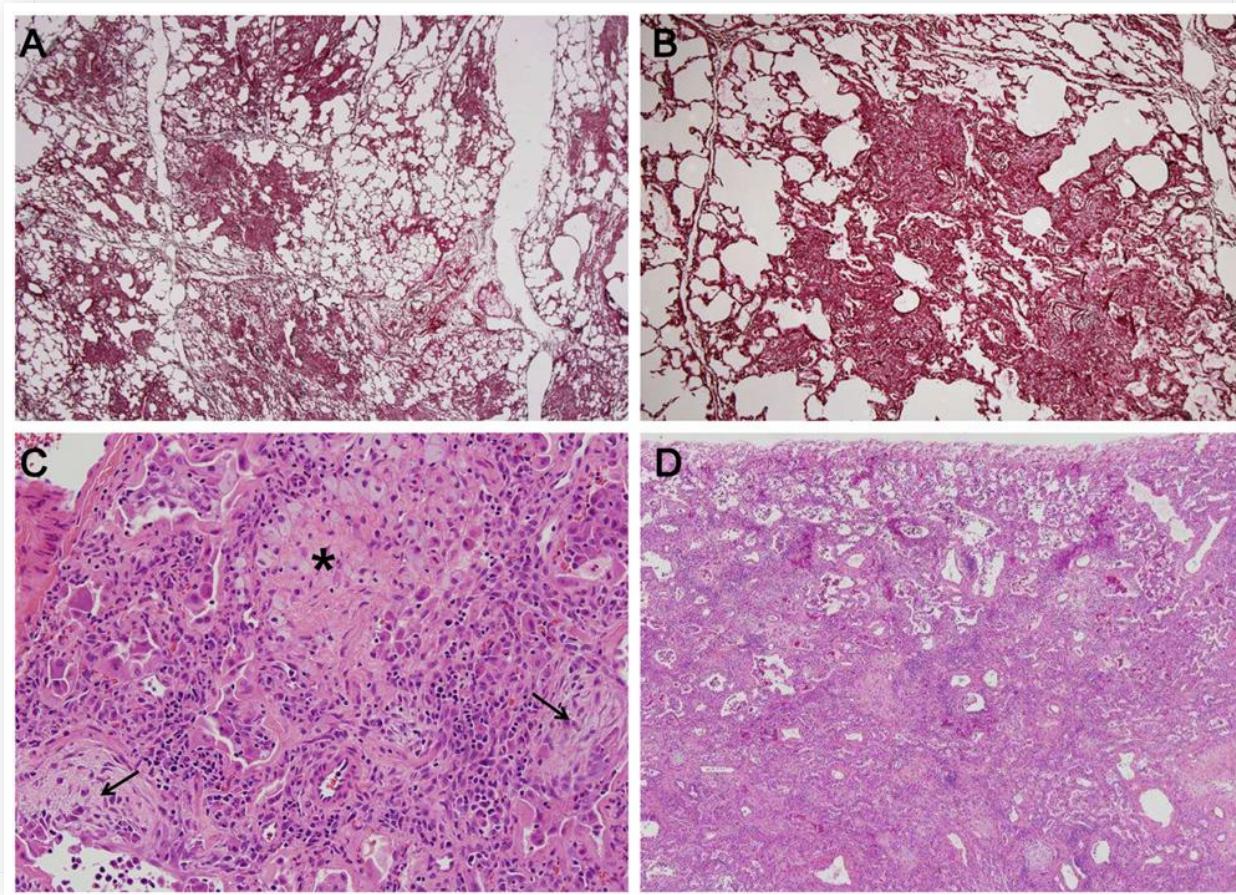
- An infective aetiology was initially suspected.
- Epidemiological investigation (a hospital based case-control study) revealed that all patients had used humidifier disinfectant in their homes.
- It transpired that children had also been affected.

- From 2006 epidemics of fatal lung injury in children were observed in Korea every spring (14).
- Clinical characteristics of suspected cases between 2006-2011 were reviewed and association with humidifier disinfectant use made.
- 138 cases, average age 30.4 months. 80 children died.
- No new cases following humidifier disinfectant ban in 2011.

- Mechanism by which polyhexamethylene guanidine phosphate, poly(oxyalkylene guanidine) hydrochloride, chloromethylisothiazolinone/methylisothiazolinone (toxic materials within humidifier disinfectant) not yet known.
- Avoidable? Writing about 'Humidifier fever' in Parkes third edition (1994) Pickering stated (use of humidifier biocides) "should be discouraged because we have no knowledge of the effects of long-term exposure to this group of chemicals"



3/52 from onset, patchy consolidation. B: 1/12, diffuse centrilobular ground-glass attenuation. C: 1 year, diffuse centrilobular fibrosis. D: 5 year old girl, severe disease, pneumomediastinum, pneumothorax, subcutaneous emphysema. (14)



A: centrilobular interstitial thickening and fibrosis. B: Bronchiolo-centroc destruction. C: Inflammatory infiltration and fibroblastic proliferation within alveolar septa and bronchioles. D: Loss of airspaces because of interstitial thickening and fibrosis. (14)

MCQS

**WHICH OF THE
FOLLOWING IS TRUE
OF THE ANATOMY OF
THE LUNG?**

1. The blood gas-barrier is approximately 1/25th of the thickness of a sheet of paper.
2. It's estimated that the average adult has 300 million alveoli.
3. The volume of an alveoli is 14 times that of a grain of sand.
4. All of the above.

**WHICH OF THE
FOLLOWING IS TRUE
OF SOUTH KOREAN
LUNG?**

1. It predominantly affected women and children.
2. Most adult patients did not require mechanical ventilation.
3. An infective aetiology was not initially suspected.
4. It has not resulted in legal proceedings.

**WHICH OF THE
FOLLOWING IS TRUE
OF INDIUM LUNG?**

1. Cases have reported in China, Japan, and Korea.
2. It is characterized by a single distinct pathological appearance.
3. Disease onset typically occurs after age 60.
4. Several pathological appearances are associated with Indium Lung.

SUMMARY

1. Occupational and environmental exposures change over time giving risk to new disease outbreaks; the interstitium is vulnerable
2. Recent occupational and environmental interstitial lung disease outbreaks include Ardystil, Indium tin oxide, and South Korean lung
3. The relationship between exposures and pathological patterns is frequently not 1:1
4. Stay vigilant

QUESTIONS?

QUESTIONS AND CONTACT

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- www.carlreynolds.net

REFERENCES

1. Cullinan, Paul, et al. "Occupational lung diseases: from old and novel exposures to effective preventive strategies." *The Lancet Respiratory Medicine* (2017).
2. Reynolds CJ, Blanc PD. Organising Pneumonia and Other Uncommon Interstitial Disorders in Parkes' Occupational Lung Disorders. CRC Press; 4th edition.
3. Litow, Francesca K., et al. "Occupational interstitial lung diseases." *Journal of occupational and environmental medicine* 57.11 (2015): 1250-1254.
4. Glazer, Craig S. "Occupation, avocation, and interstitial lung disease." *Clinical Pulmonary Medicine* 18.1 (2011): 20-28.
5. Wallis, Adam, and Katherine Spinks. "The diagnosis and management of interstitial lung diseases." *Bmj* 350 (2015): h2072.

6. Travis, William D., et al. "An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias." *American journal of respiratory and critical care medicine* 188.6 (2013): 733-748.
7. King TE. Approach to the adult with interstitial lung disease: Clinical evaluation. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2015.
8. West, John B. "Role of the fragility of the pulmonary blood-gas barrier in the evolution of the pulmonary circulation." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 304.3 (2013): R171-R176.

9. McNulty, William, and Omar S. Usmani. "Techniques of assessing small airways dysfunction." European clinical respiratory journal 1 (2013).
10. Coultas, David B., et al. "The epidemiology of interstitial lung diseases." American journal of respiratory and critical care medicine 150.4 (1994): 967-972.
11. Tarlo, Susan, Paul Cullinan, and Benoit Nemery, eds. Occupational and environmental lung diseases: Diseases from Work, Home, Outdoor and Other Exposures. John Wiley & Sons, 2011.
12. Hoet, P. H., et al. "In vitro cytotoxicity of textile paint components linked to the" Ardystil syndrome"." Toxicological Sciences 52.2 (1999): 209-216.

13. Cummings, Kristin J., et al. "Indium lung disease." *CHEST Journal* 141.6 (2012): 1512-1521.
14. Kim, Kyung Won, et al. "Humidifier disinfectant-associated children's interstitial lung disease." *American journal of respiratory and critical care medicine* 189.1 (2014): 48-56.
15. Hong, Sang-Bum, et al. "A cluster of lung injury associated with home humidifier use: clinical, radiological and pathological description of a new syndrome." *Thorax* (2014): thoraxjnl-2013.