# 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/*

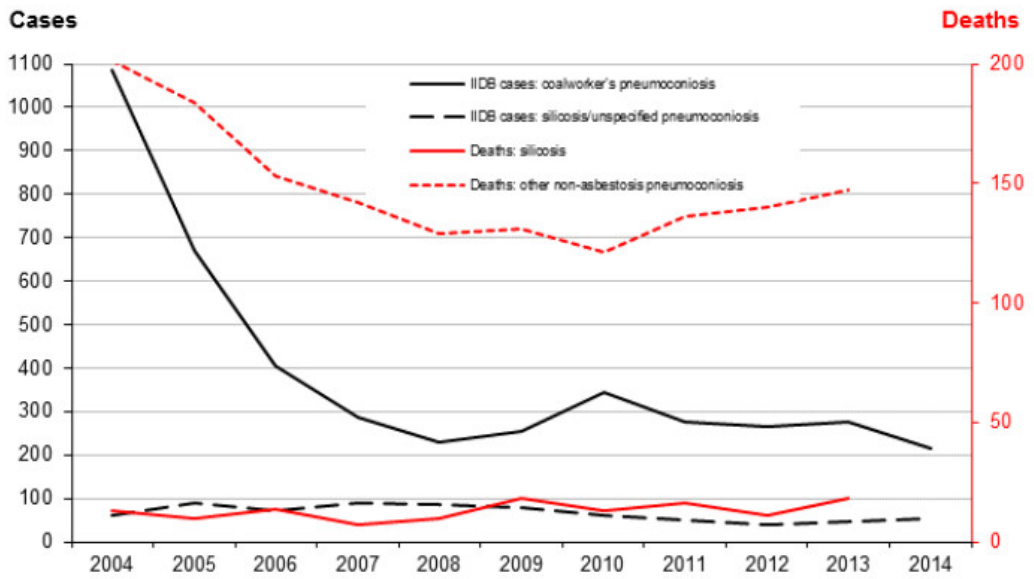
- additional material available

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

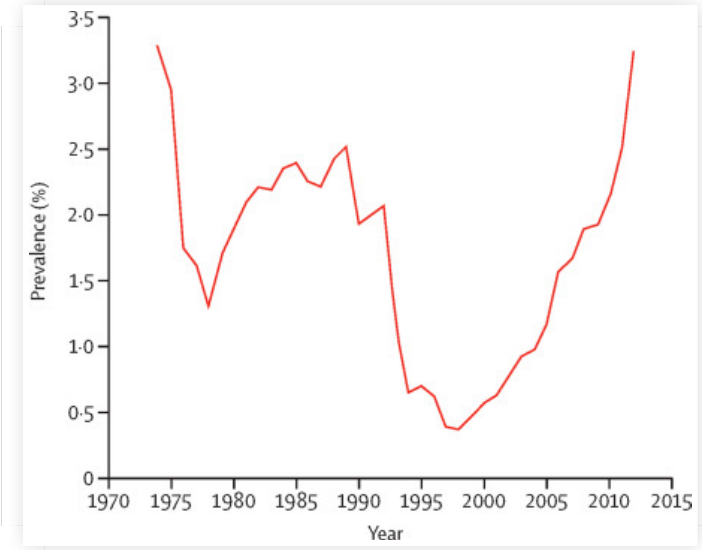
# BEYOND PNEUMOCONIOSIS?

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?

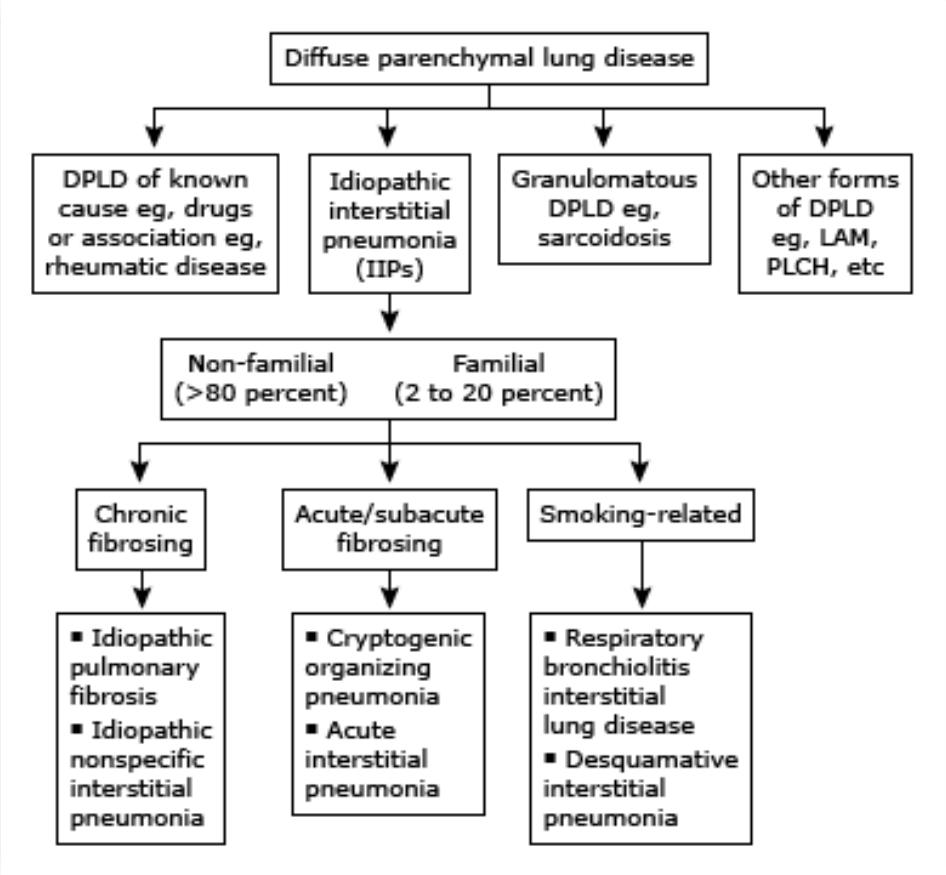
# DEFINITIONS

# WORK-RELATED DOESN'T MEAN OCCUPATIONAL

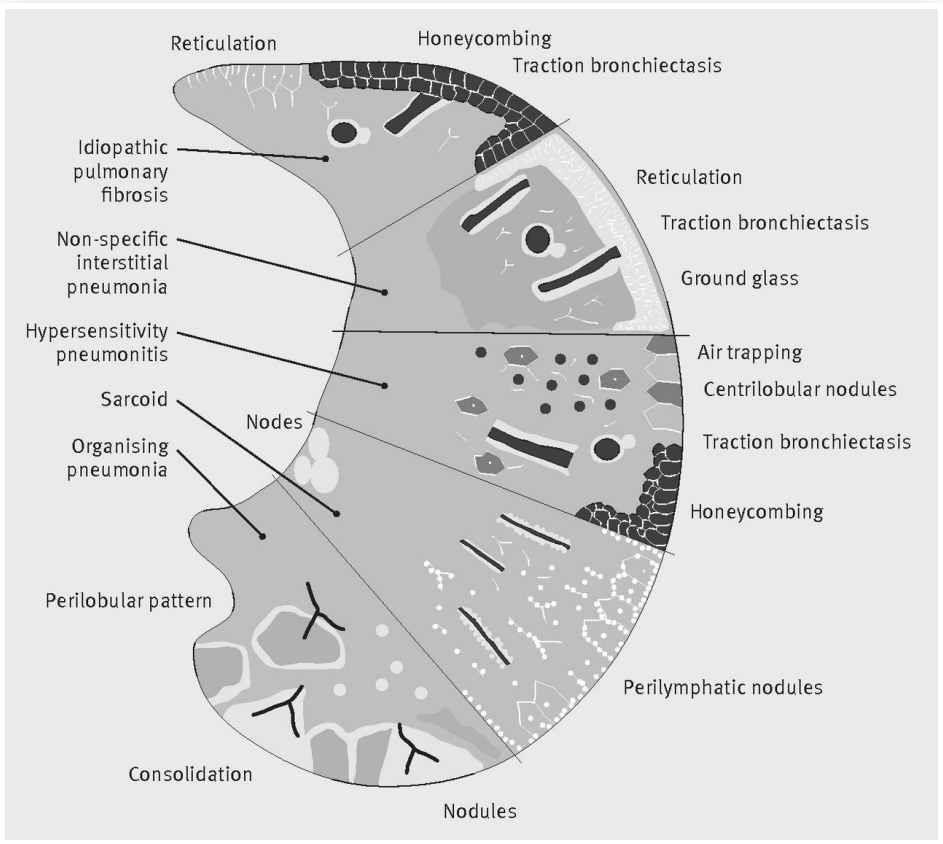
- occupational diseases are primarily caused by exposure to risk factors arising from work
- work-related diseases have multiple causes; factors in workplace may play a role (WHO 2017)

# 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



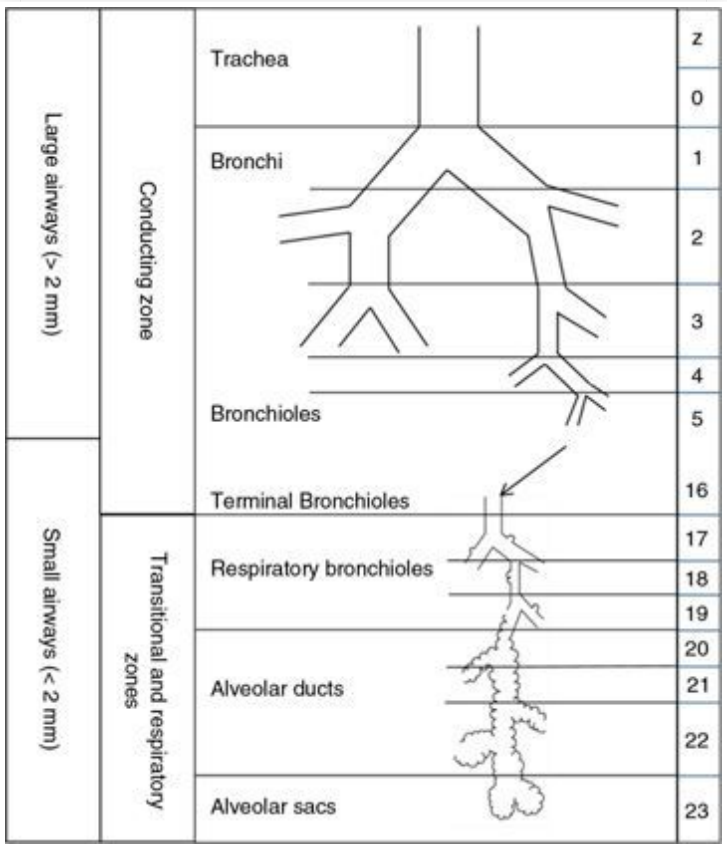

An ILD Taxonomy (7)




# CT appearance ILD (5)

# LUNG PHYSIOLOGY AND INTERSTITIAL EXPOSURES

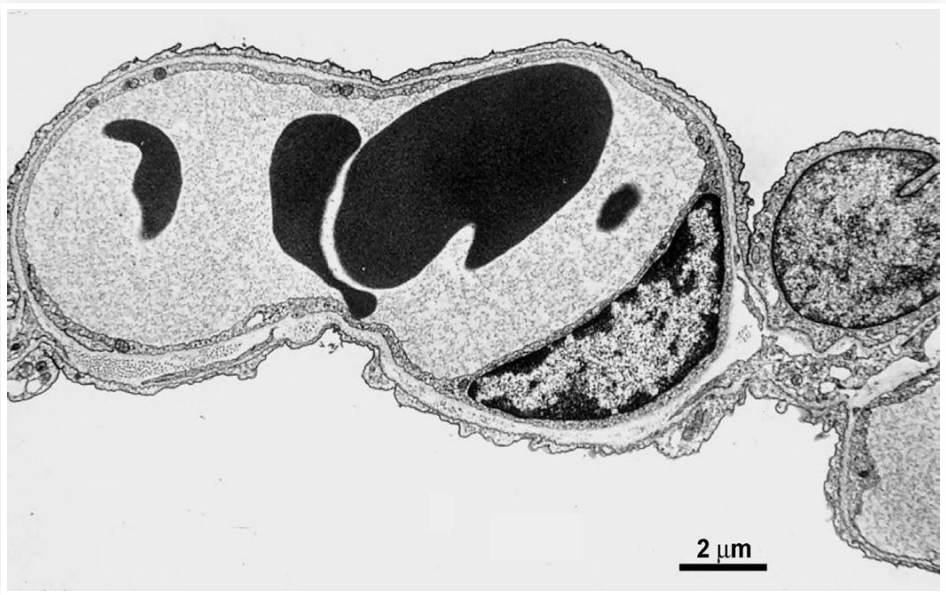
- Diffusion of gases across blood-gas barrier is passive and governed by Fick's Law.




Weibel model

*Vgas (diffusing) is proportional to Area/Thickness * D(diffusion constant) * (P1 - P2)*

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




Blood gas barrier

- 2µm across (for ref sheet of paper is 50µm, 1/20th of a mm or 0.05mm). (17)
- 25x 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).(16) Surface area of a tennis court.
- basic tripartate layout highly conserved throughout evolutionary history (alveolar epithelium, ECM, capillary endothelium, seen American lungfish arising some 400 million years ago) (18)

*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

- particles > 2μm in diameter deposit in the larger airways
- particles 1-2μm the smaller conducting airways
- particles 0.1-1μm deposit in the alveolar-interstitial region

- the 0.1-1μm range includes paint pigments, metal dusts, and humidifier particles
- responses to exposure can be divided e.g irritant/fibrotic /allergic/infectious/carcinogenic

# WORK-RELATED ILD

# ILD INCIDENCE 30/100,000 PER YEAR

# ILD PREVALENCE 70/100,000

- 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, cadium, diacetyl, asbestos
- less common: cobalt, rare earths, plutonium

| Agent | Disease | Source |
|---|---|---|
| Microbial | | |
| Thermophilic actinomycetes, eg, *Micropolyspora faeni* | | |
| Fungus, eg, *Aspergillus umbrosus* | Farmer's lung | Mouldy hay, grain, silage |
| Thermophilic actinomycetes, eg, *M. faeni* | Mushroom worker's lung | Mushroom spores |
| *Mucor stolonifer* | Paprika lung | Mouldy paprika pods |
| Thermophilic actinomycetes | Potato riddler's lung | Mouldy hay around potatoes |
| Animal sources | | |
| Thermophilic actinomycetes | Bagassosis | Mouldy pressed sugar cane |
| *Penicillium frequentes* | Suberosis | cork |
| *Penicillium casei* | Cheese worker's lung | Cheese |
| *Aspergillus clavatus* | Malt worker's lung | Whisky maltings |
| *Cryptostroma corticale* | Maple bark stripper's disease (coniosporosis) | Maple bark |
| Feathers, serum proteins on pigeons, budgerigars | Bird fancier's lung | Birds |
| Serum proteins | Poultry worker's lung | Poultry birds |
| *Sitophilus granarius* (wheat weevils) | Miller's or wheat weevil's lung | Dust-contaminated grain |
| Fish meal | Fish meal worker's lung | Fish meal dust |
| Pituitary proteins (cattle, pig) | Pituitary snuff taker's lung | Pituitary snuff |
| Urinary proteins | Rodent handler's lung | Rodents |
| Chemicals and miscellaneous | | |
| Probable microbial contamination | Humidifier fever/ ventilation pneumonitis, sauna user's lung, air conditioner lung disease | Miscellaneous |
| Sodium diazobenzene sulfate | Pauli's reagent alveolitis | Pauli's reagent |
| Isocyanates | Isocyanate lung | Many, including paints, foams, polyurethane products |
| Unknown | Coffee worker's lung | Coffee bean dust |
| Avian proteins | Feather duvet lung | Feather beds and duvets |
| Probable bacterial contamination | Metalworking fluid lung | Metalworking fluid |

# Causes of hypersensitivity pneumonitis (19)

# RELATIONSHIP BETWEEN AETIOLGIC 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.

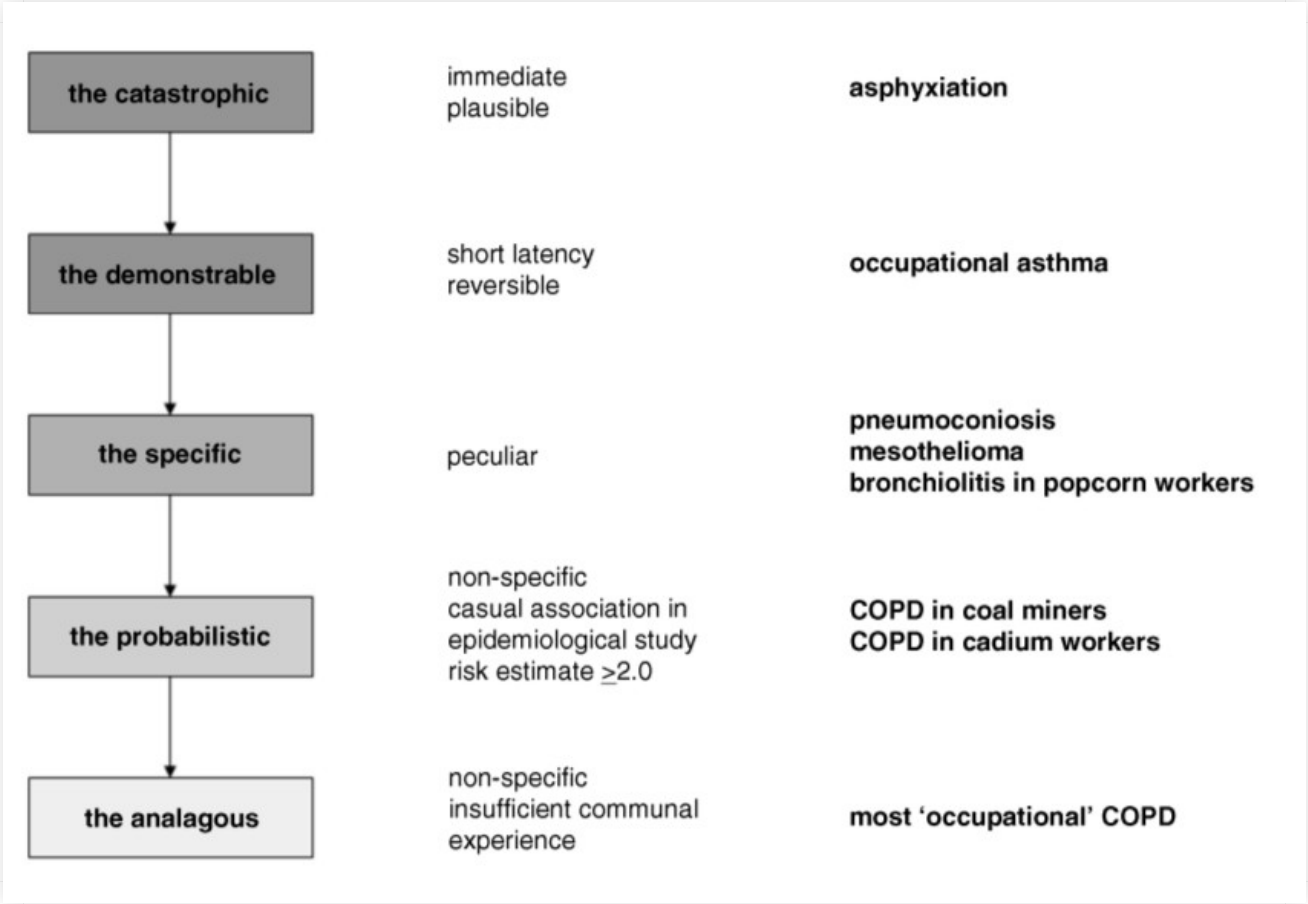
# Pathologic Patterns and Causes (4)

# 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

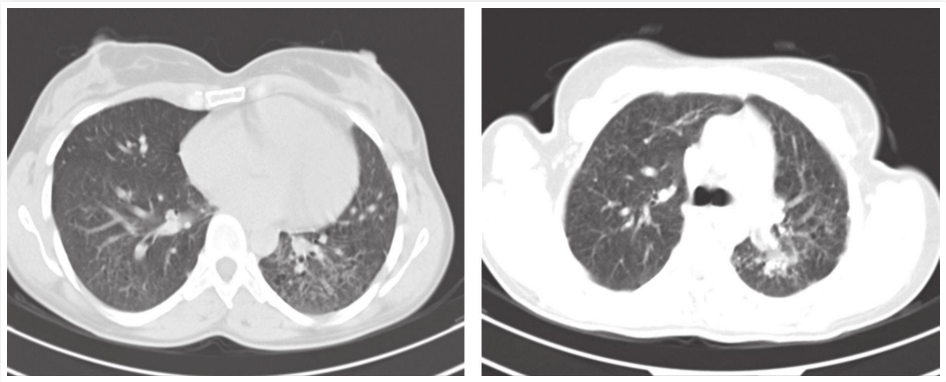
# THREE RECENT OUTBREAKS

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

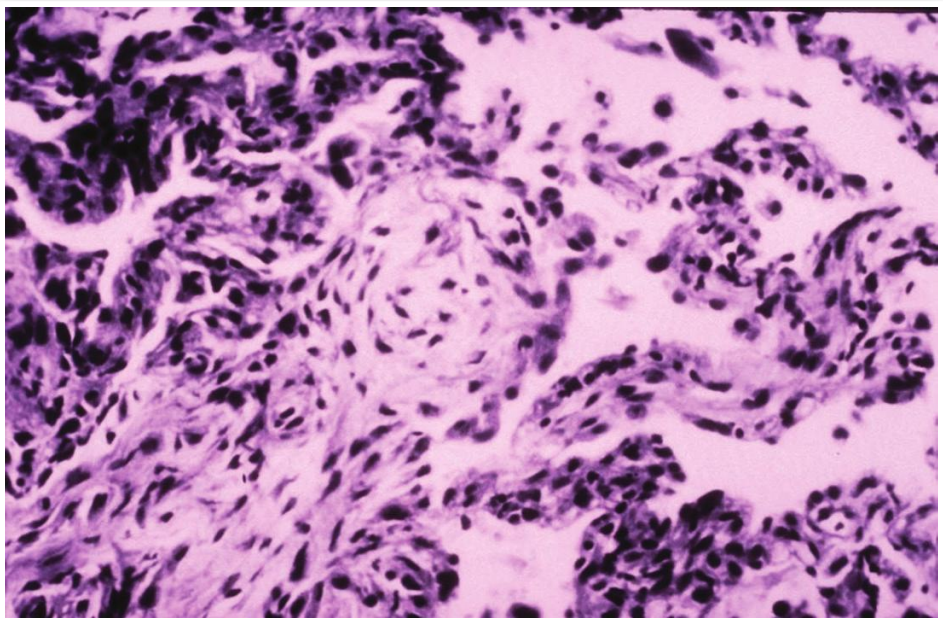
# ARDYSTIL

- 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.

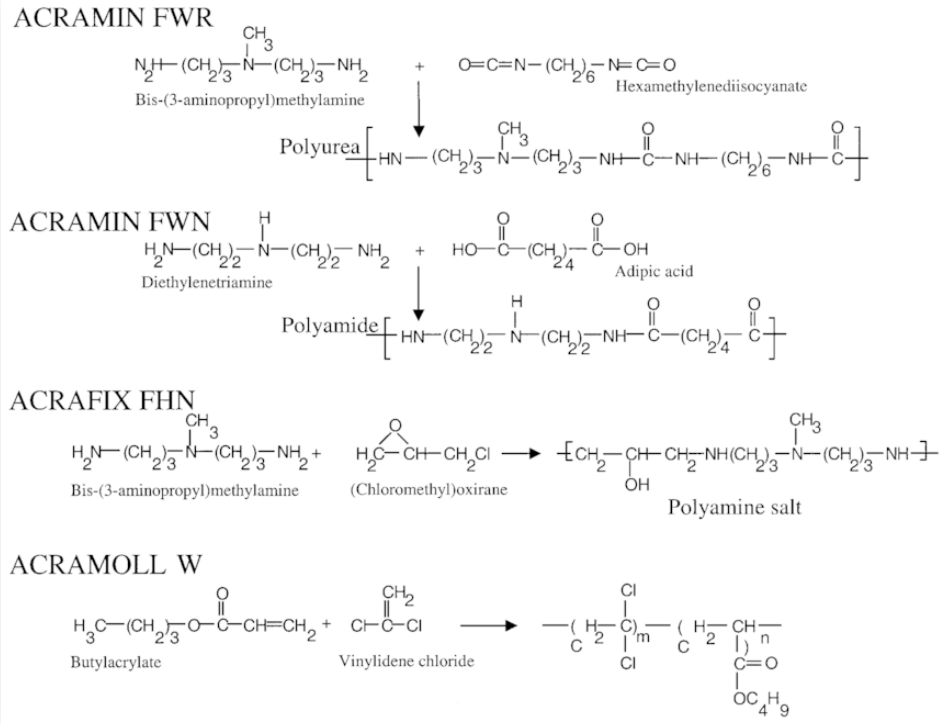
- Factory A had the highest risk of being a case (RR=24.3; 95% Cl=5.7-104.4), followed by Factory B (RR=11, 95% CI=11.9- 62.9) and only two out of 22 cases had never worked in factories A or B.
- It was found that only in factories A and B had the presence of an airborne chemical by the trade name Acramin FWR that had recently been substituted with another related compound Acramin FWN.
- Similar outbreak occurred later in the same year in Algeria. 5 cases among 12 textile workers air-spraying with "products from spain", 1 fatality.(20)



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)

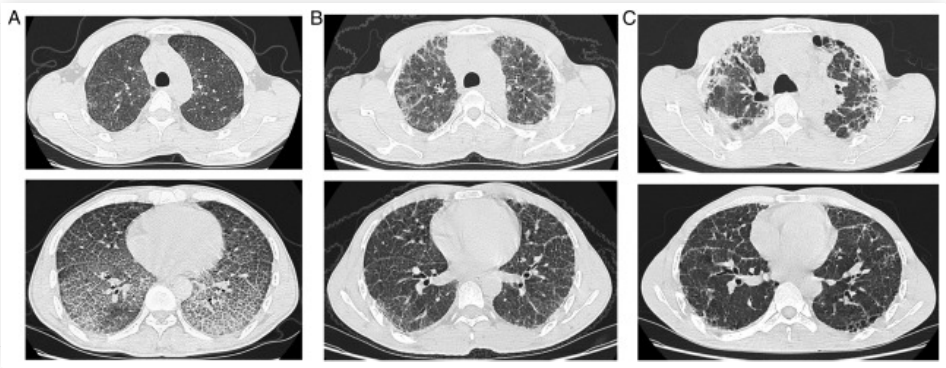



Chemical structure of Acramin FWN and Acramin FWR (12)

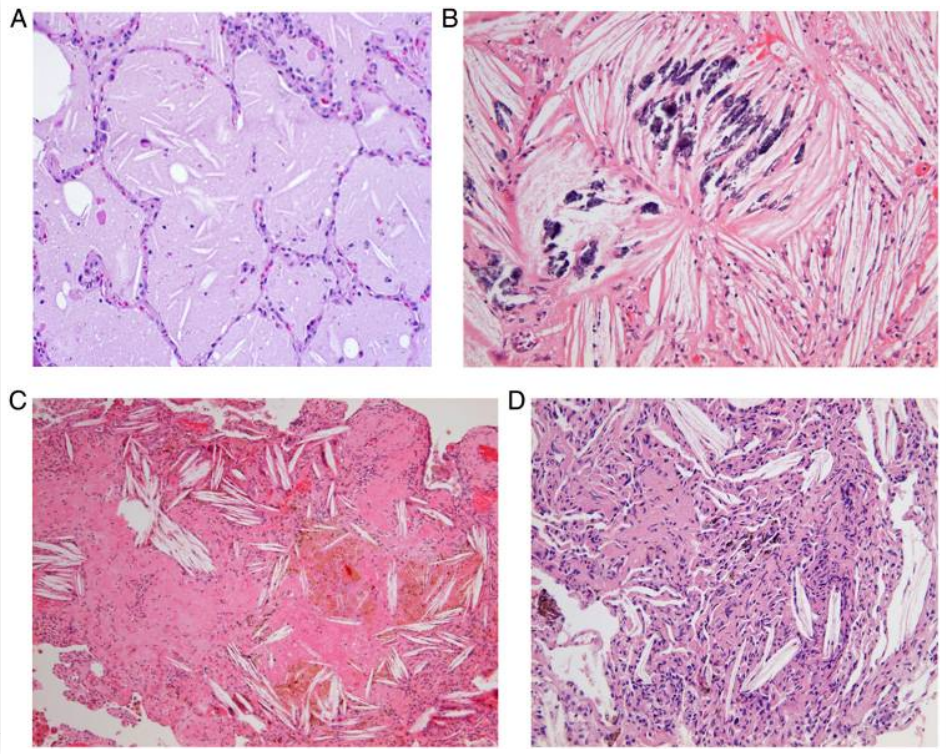
- Acramin FWR (tradname Ardystil) recently introduced as a replacement for Acramin FWN at the two factories where majority of cases had worked.
- Animal studies confirmed respiratory toxicity.
- Thought that highly negatively charged long-chain molecular structure of Acramin FWN contributes causes toxicity.

# 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 Ardystil 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 histopatholgical features. A-C features of alveolar proteinois. D multinucleated giant cells, interstitial fibrosis, and brown particles composed predominantly of indium. (13)

# SOUTH KOREAN LUNG

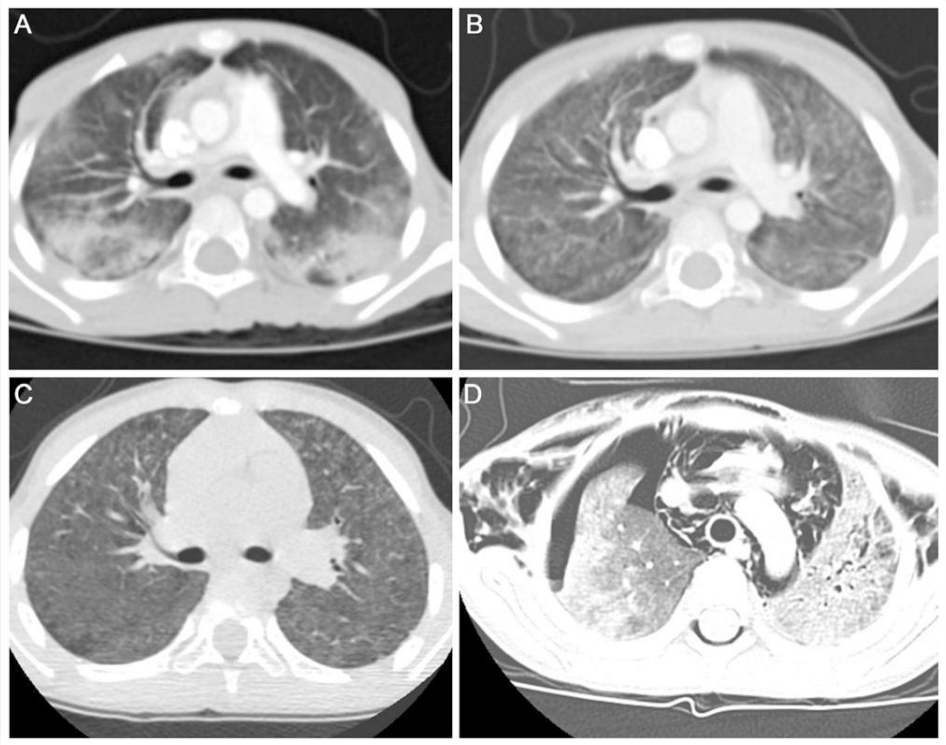

''A former South Korean executive of UK-based Reckitt Benckiser has received a seven-year prison sentence over a humidifier disinfectant linked to the death of around 100 people''. BBC News website (accessed Jan 17 2017)

- Household clustering (6 cases belonged to household clusters e.g had a partner or children also affected) 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.

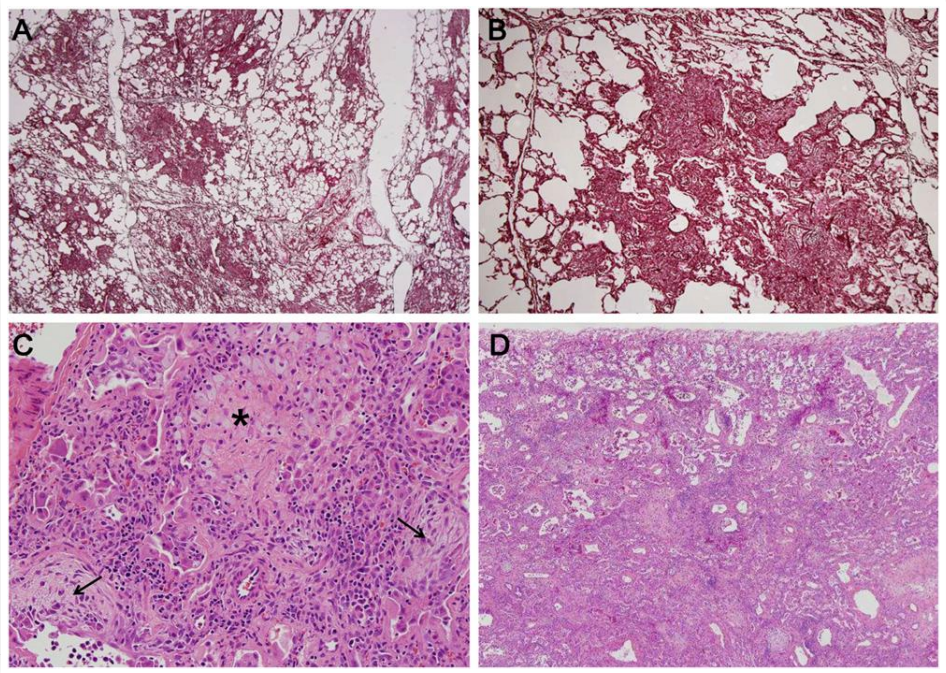
- An infective aetiology was initially suspected (because recent viral epidemics)
- Epidemiological investigation (a hospital based case-control study) revealed that all patients had used humidifier disinfectant in their homes.
- Cases defined as age 20-54, characteristic radiological appearance, no alternative diagnosis. Controls from O&G, pulmonary, and allergy outpatients.
- OR for HD use = 47.3 (95% CI 6.05 - 369.7, $P < 0.01$)
- 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.
- Case-control (controls lobar pneumonia, asthma, or healthy) study found OR for HD use = 2.73 (95% CI; 1.41–5.90, P = 0.00)
- 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 Parke's 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: Bronchiolocentroc 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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