The cause of the scarring in your lungs may be coal mine dust, and it may be treatable….

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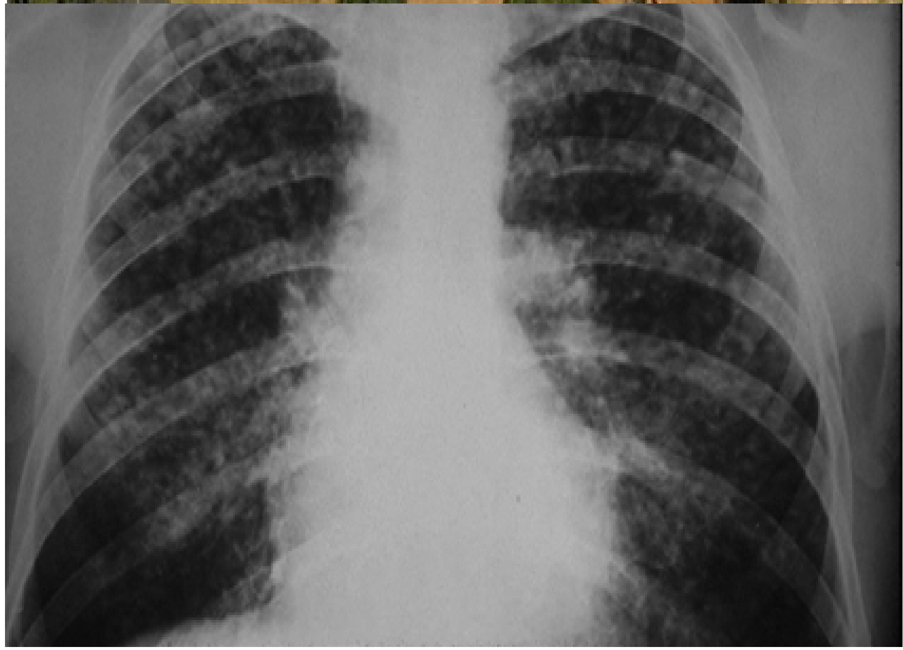
Respiratory Physician

St Vincent's Hospital, Sydney & Holdsworth House Medical Practice (HHMP),

Darlinghurst, NSW 2010

Outline of talk

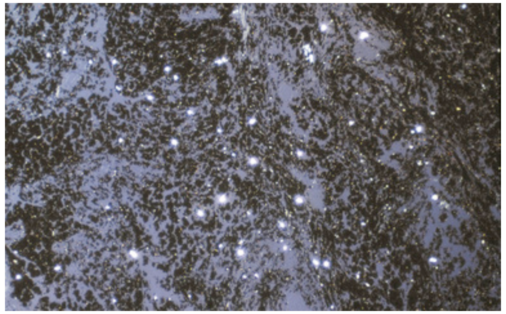
- Background
- A voyage through the lung
- Some basic mechanisms of disease
- Possible treatments
  (including anti-fibrotic agents)
- Conclusions



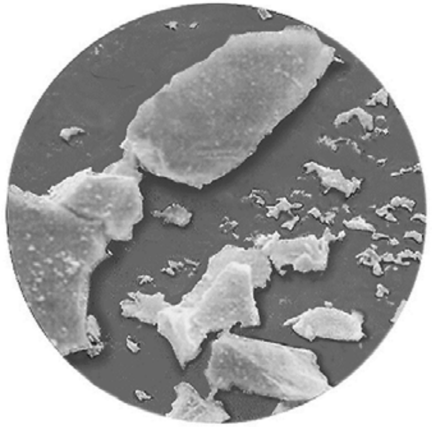
NB. Reminder of medi-speak:

pneumoconiosis = lung fibrosis due to dust (pneumo= lung; koniosis = dust (Gk)

Introduction



- Background: scarring of the lungs and its detection
- Pathways to scarring
- A trip through the respiratory system
- Lessons from other respiratory diseases
- Potential treatments including anti-fibrotic agents
- Future approaches….?



The lungs and the environment

- Work takes up most of our lives
- The environment is a key factor in the development of many diseases
- Symptoms resulting from an exposure can take many years to occur (long latency)
- Lungs are relatively resistant to disease
- Lungs have extra capacity and symptoms only occur once disease is well established; early intervention is key
- Lungs tend to react to different dusts in a similar manner
- The reaction is to a "build up"
- Dusts know no borders!

Humans and work

Traditional employment:
working the land

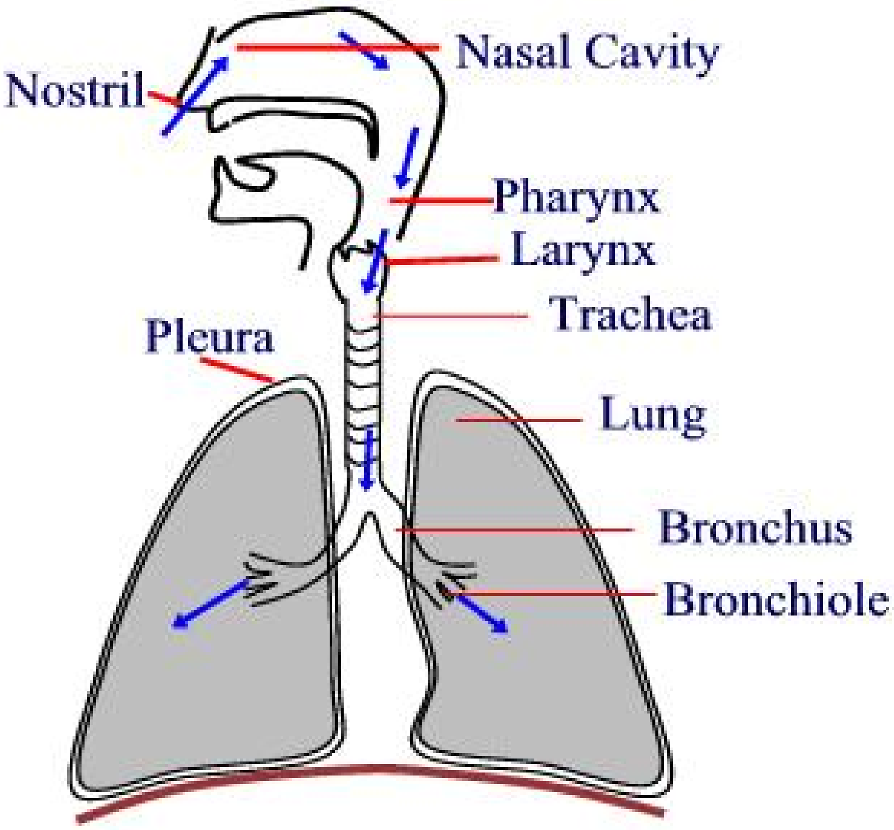
Traditional employment: work in the home

Wherever there is dust.....

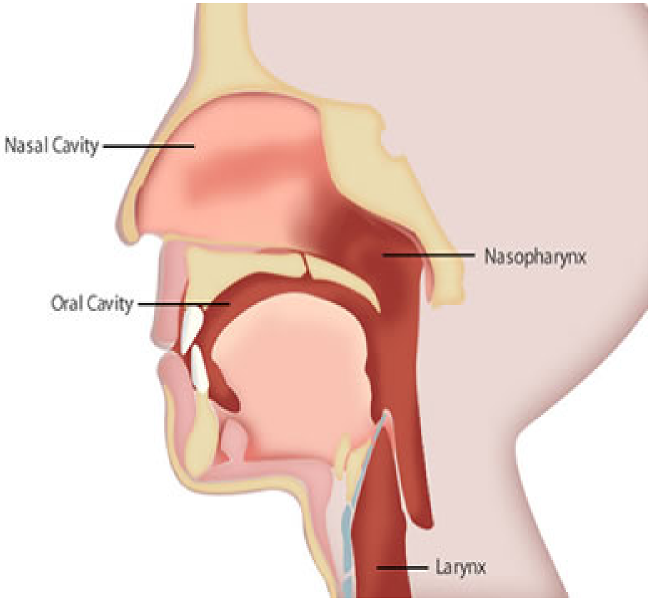
there is lung disease…

The most common causes of respiratory death and disease today….are largely preventable

The lungs: basic anatomy

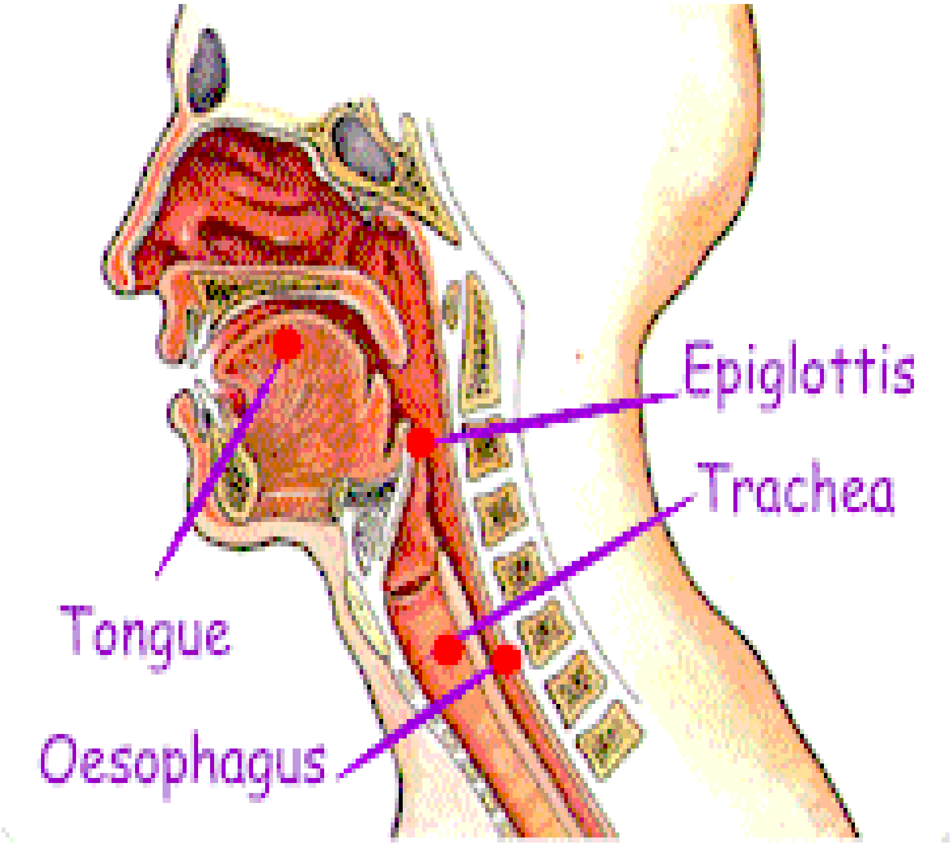


The nose

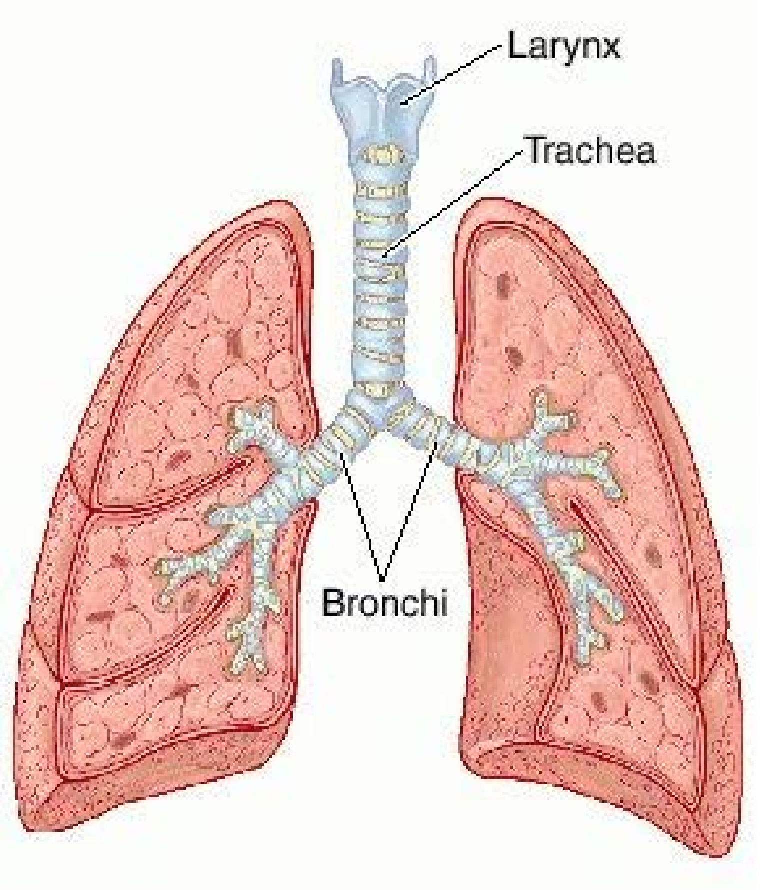


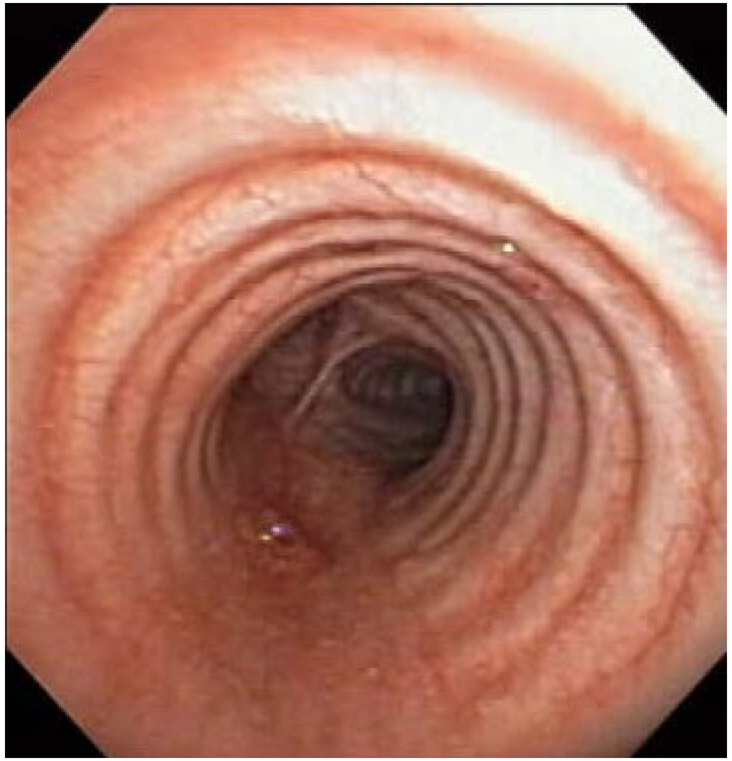
The nose traps most dust particles

The voicebox (larynx)

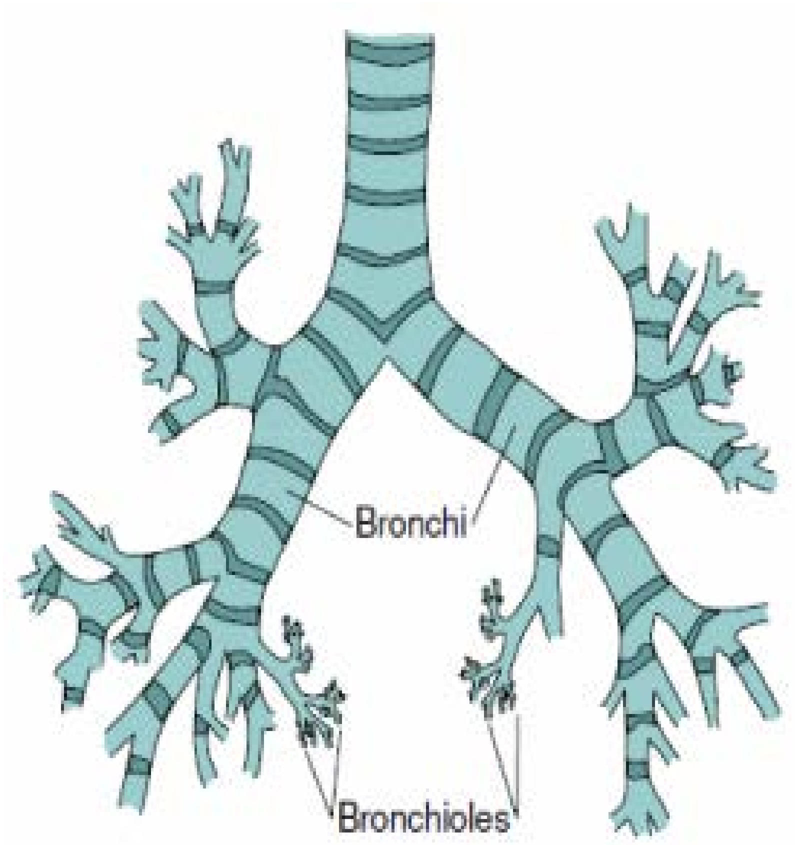


Trachea

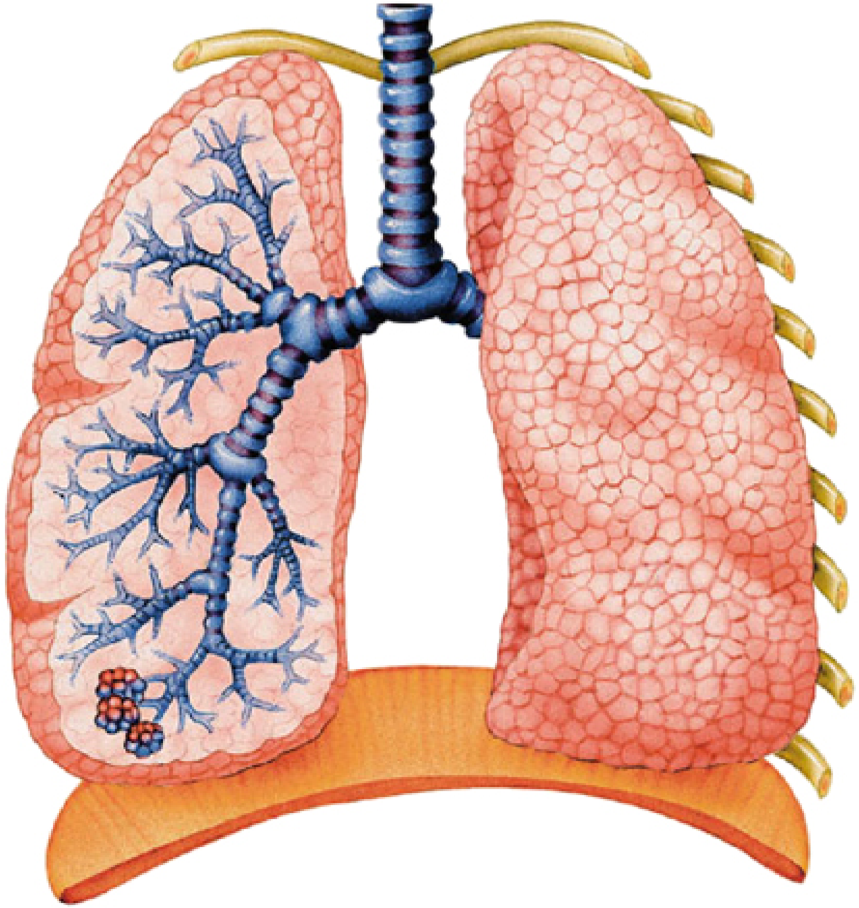


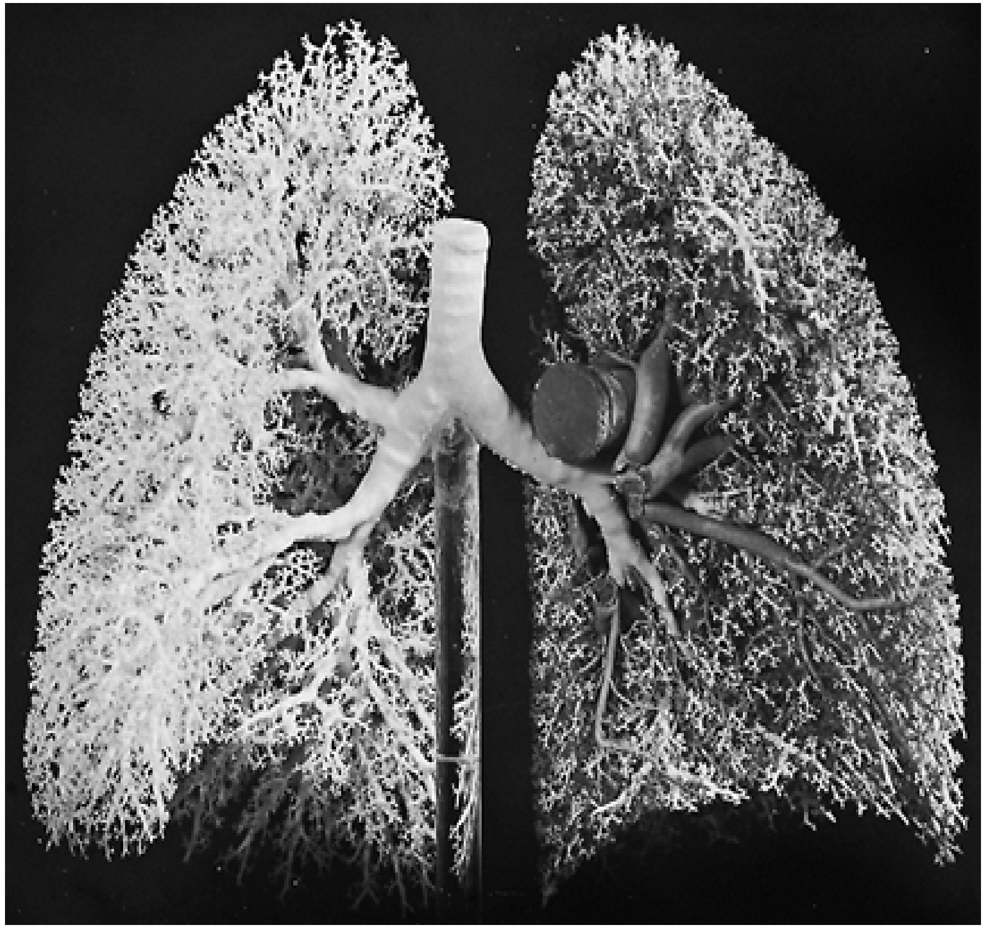


Bronchi (lung tubes)



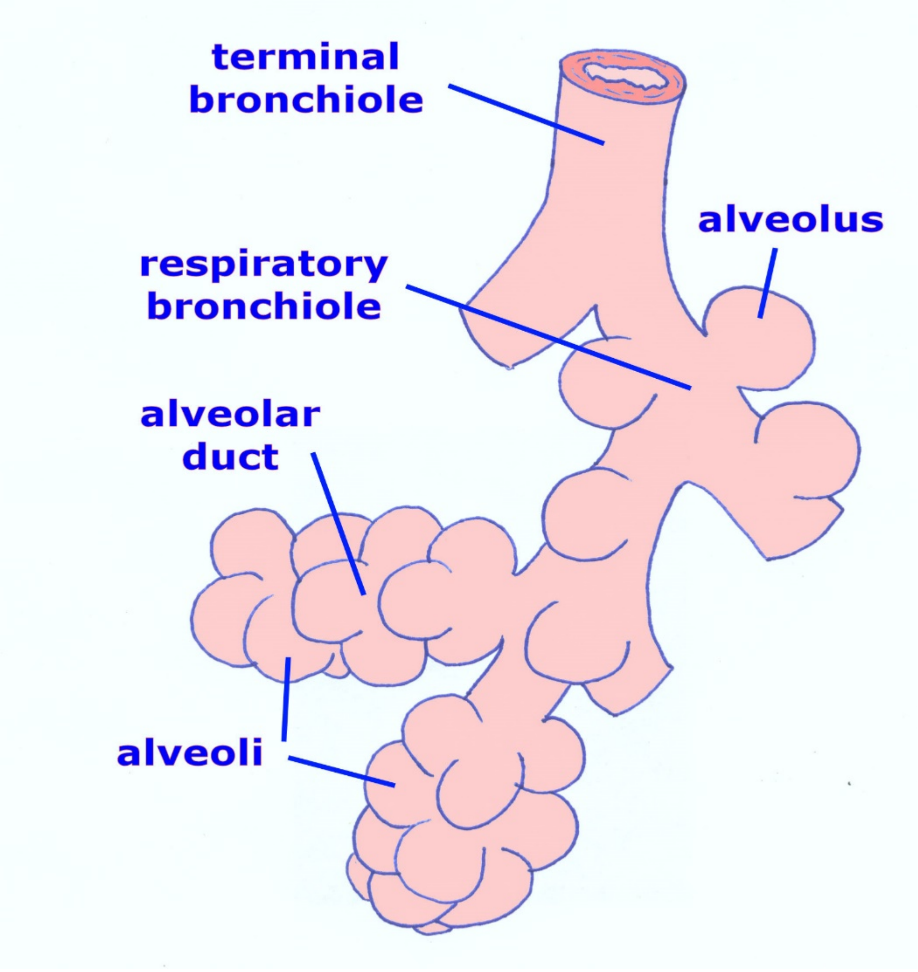
Alveoli

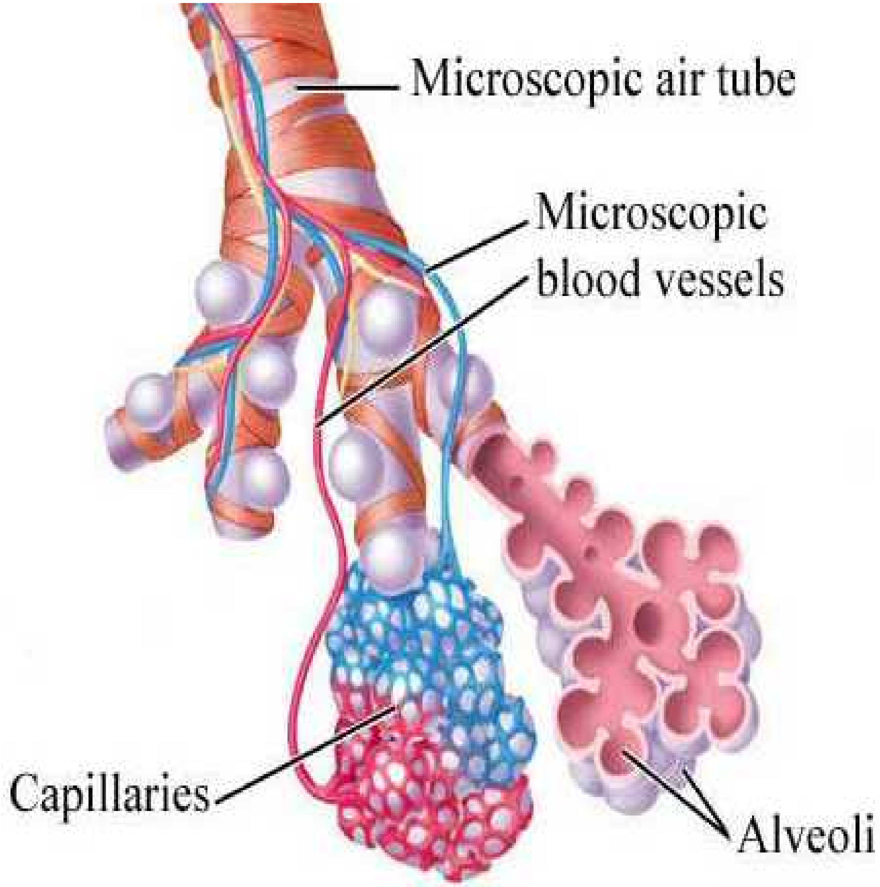




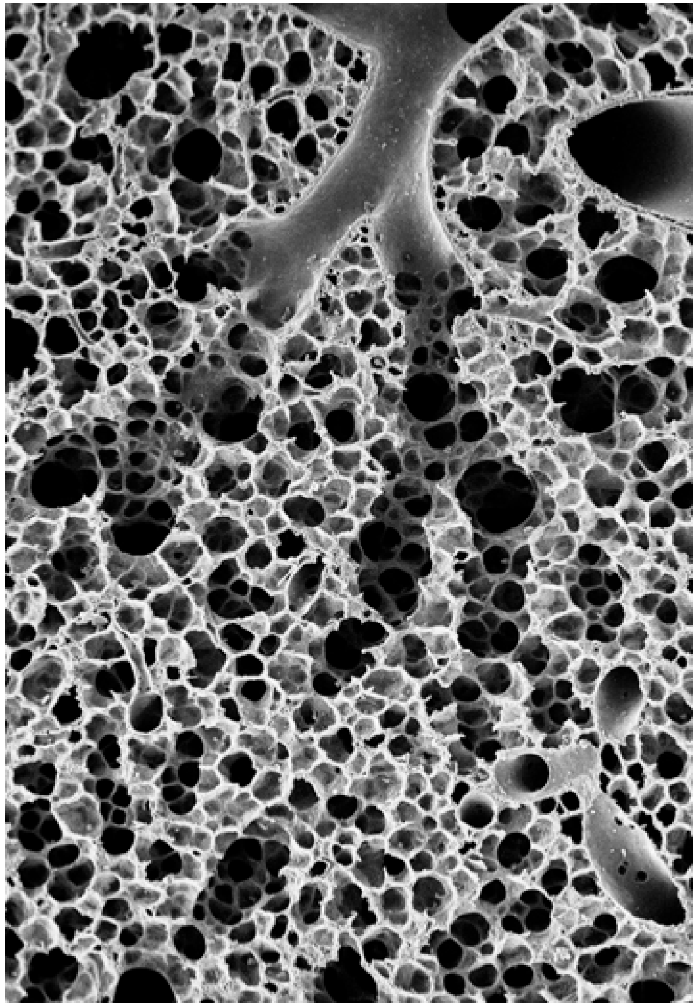
Alveoli: where gas exchange occurs

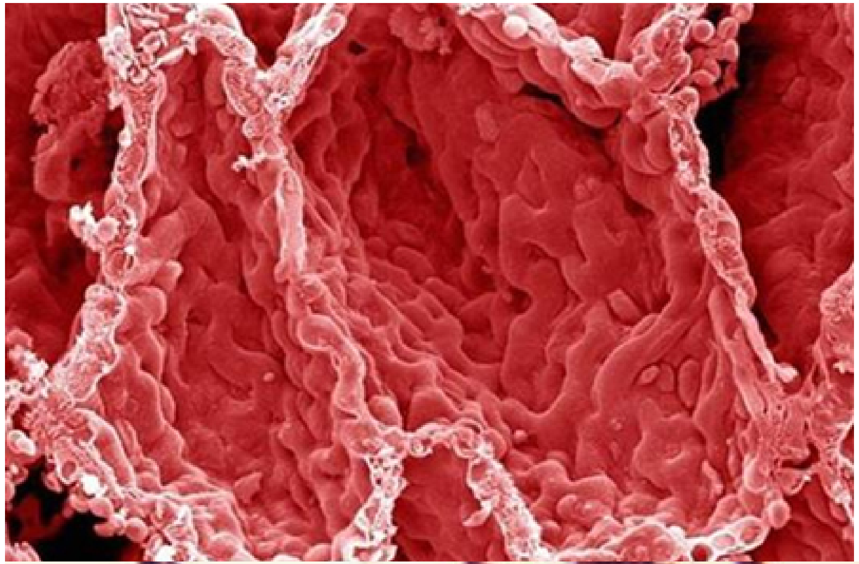
…and where fibrosis/scarring starts

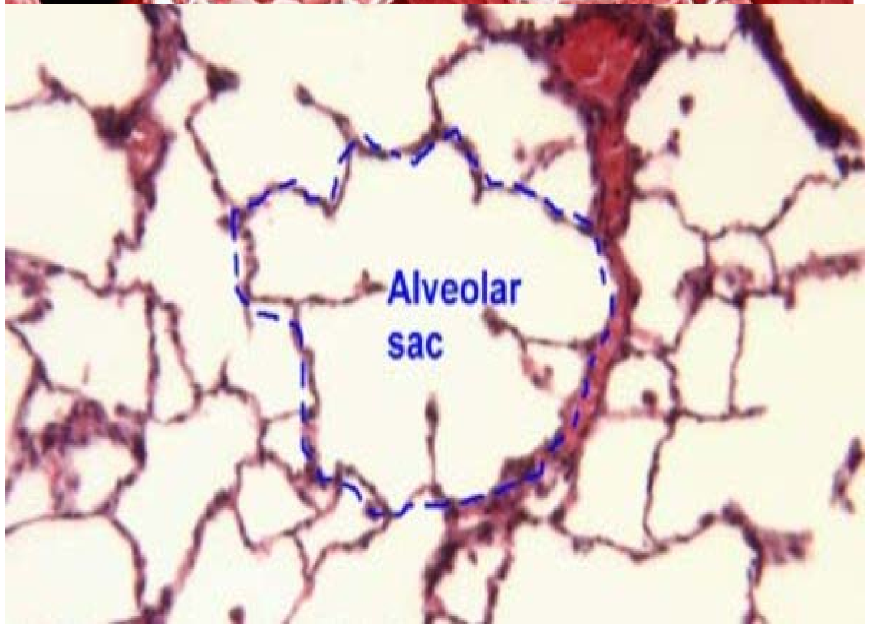




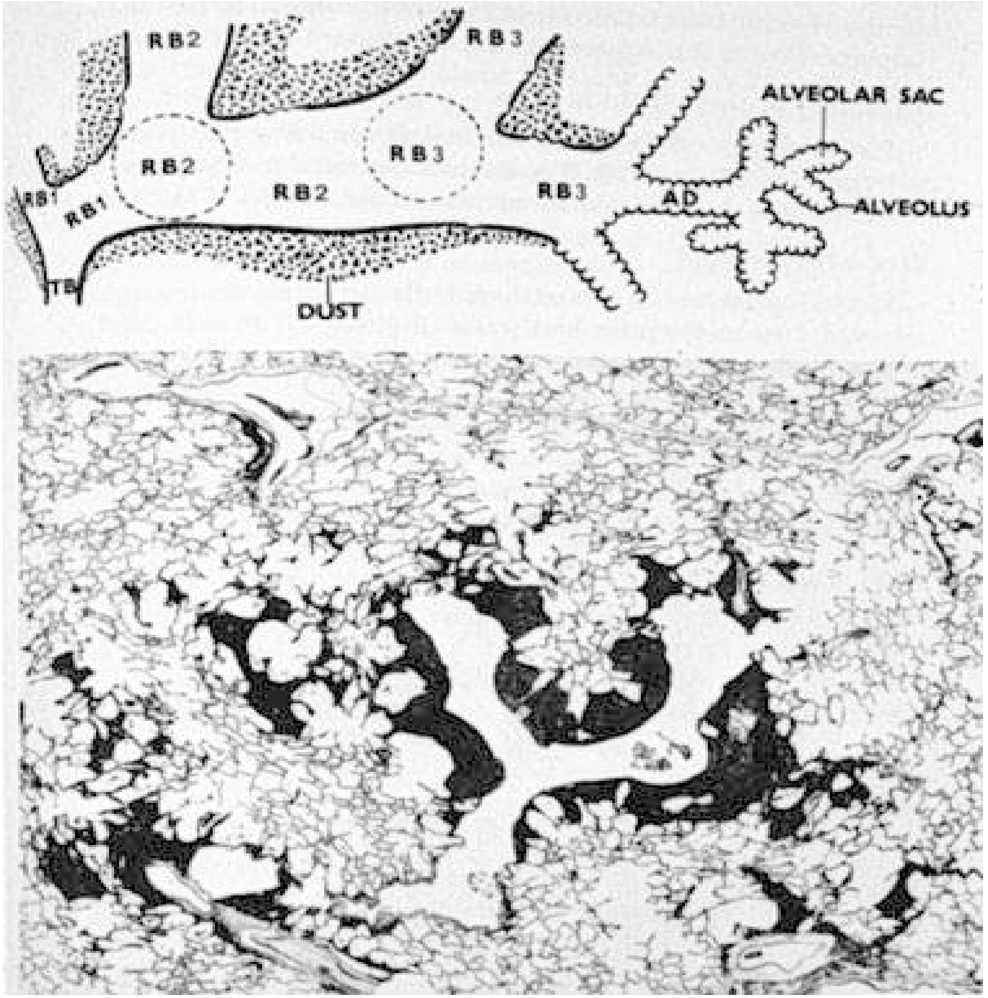
Alveoli: where gas exchange occurs

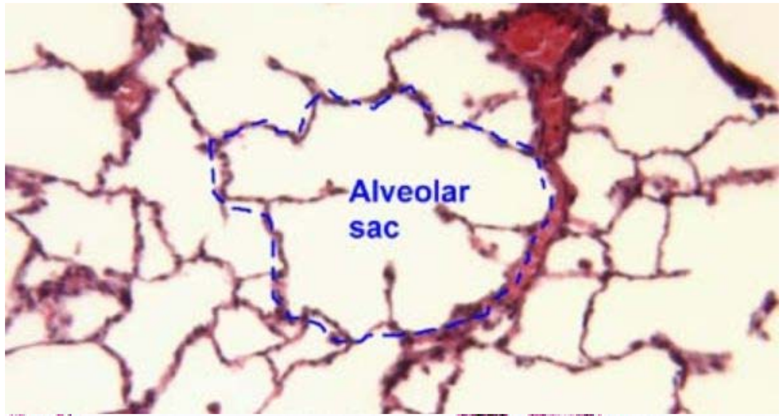


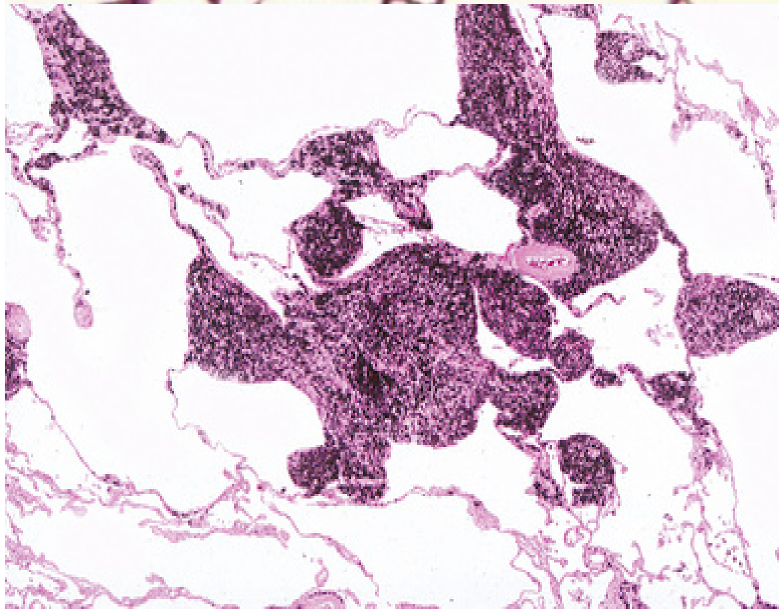




Coal dust collects around the respiratory bronchioles ie deep within the lung







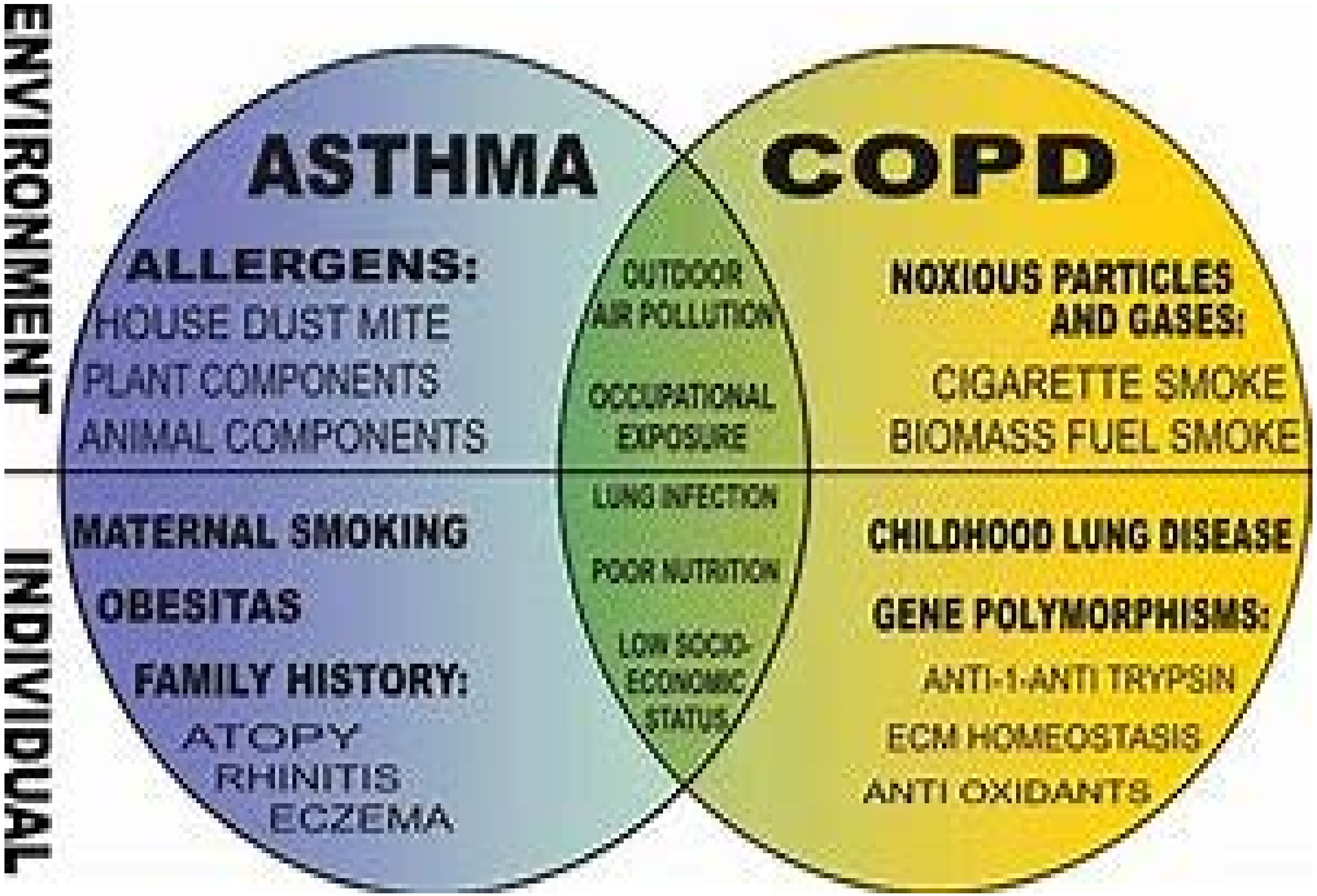
How do we assess the lungs?

- Talk to the patient and get a full history of all past workplace exposures and any potential problems (work-related or otherwise)
- Examine the patient for abnormalities
- Ensure that the information is well documented and kept for the future
- Do tests e.g CXR, bloods, lung function
- Keep records of these results

The commonest causes of lung function changes: important and treatable!

- Asthma
- COPD

(Chronic bronchitis & emphysema)

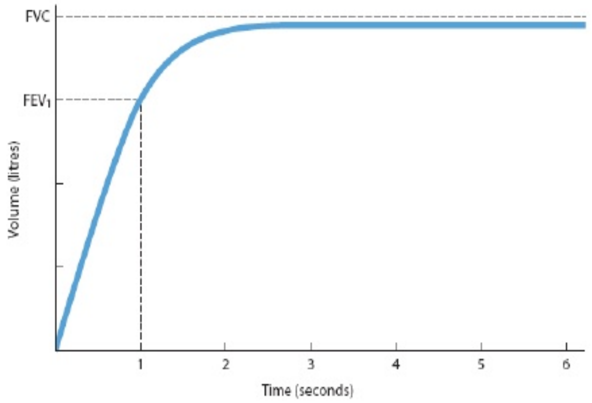


Lung function: spirometry (GP)

Spirometry

The volume/time curve

- A normal volume/time curve has a typical shape. There is a rapid rise to the trace as three-quarters of the air is expired in the first second
- The trace plateaus between 4 and 6 seconds



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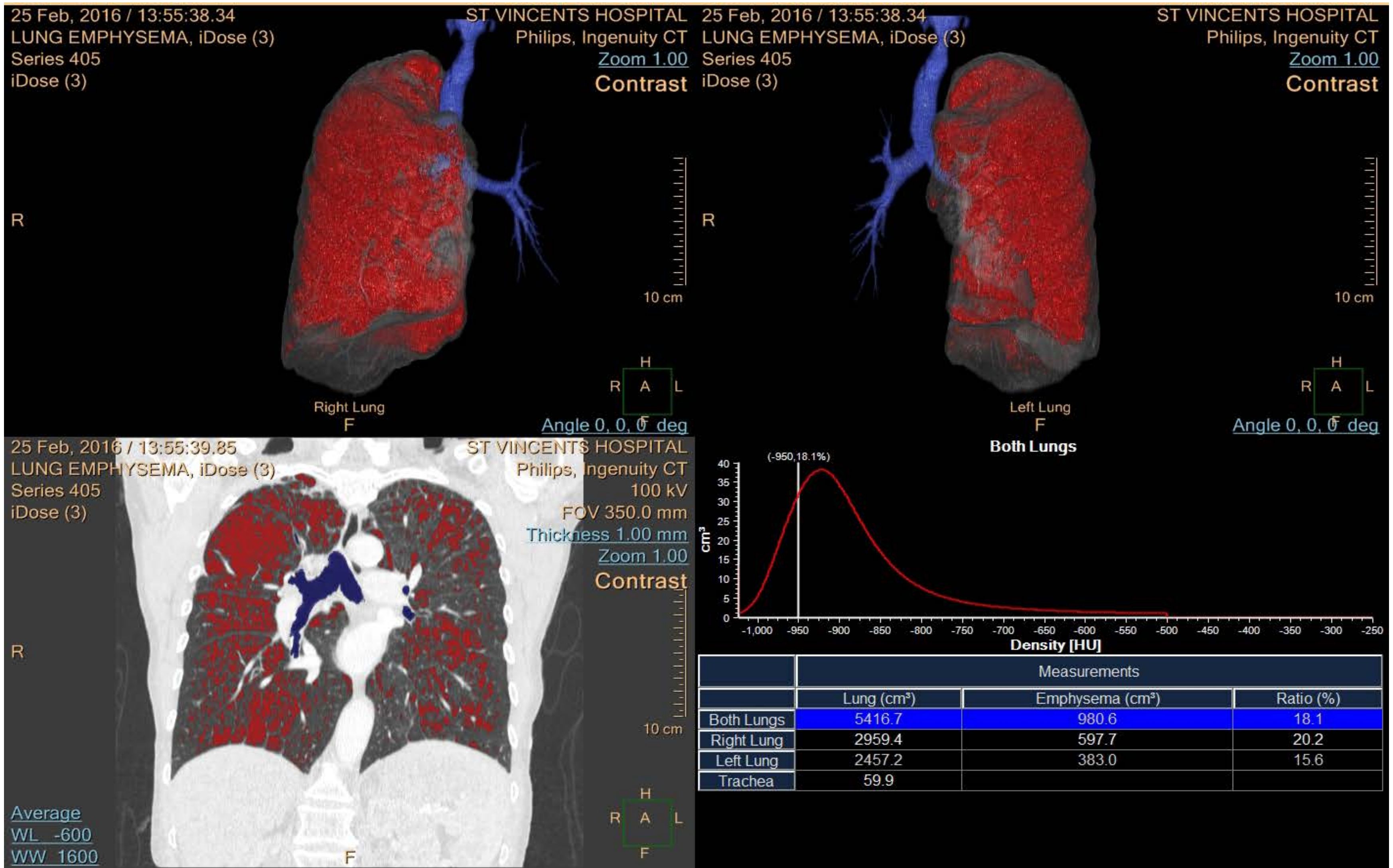
More sophisticated lung function tests

CT scanning

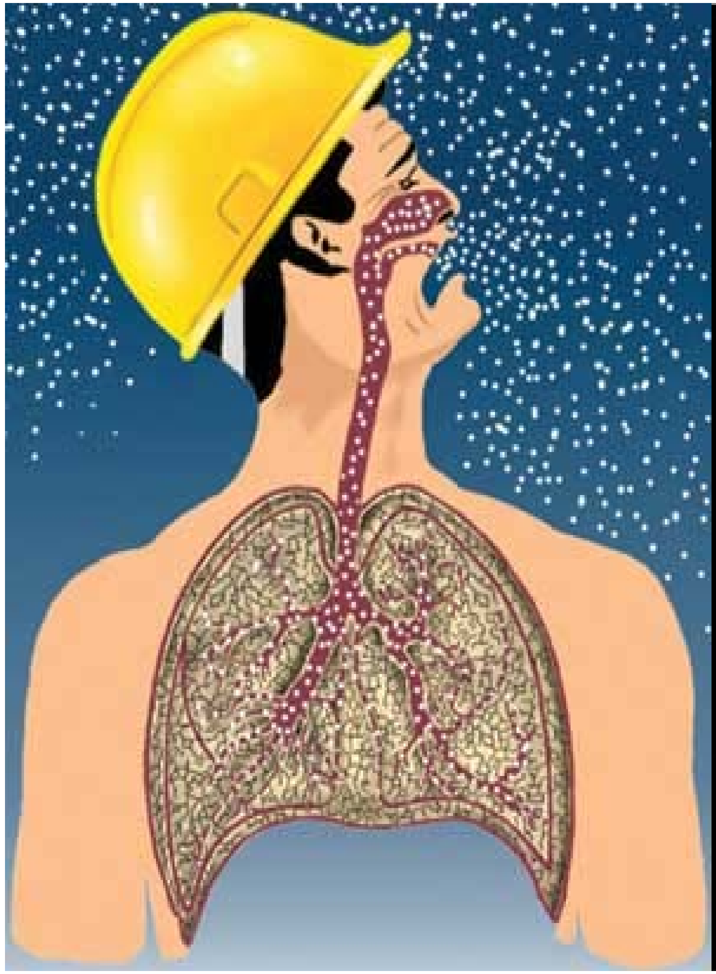
Chest X ray: less sensitive than a CT

New methods e.g. computerised software to automatically analyse CT scans



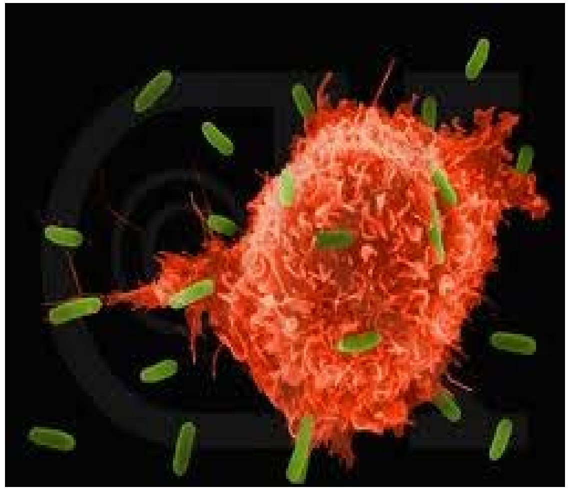
Inhaled dusts, aerosols

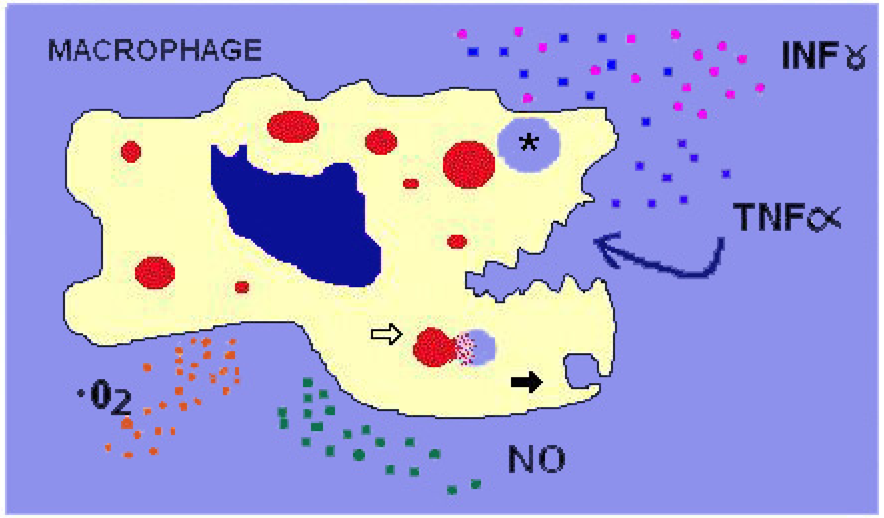
- Solid or liquid particles dispersed in the atmosphere
- Include dusts, fumes, smokes, mists and fogs
- Deposit in different parts of the lungs depending on size, electrical charge, solubility etc.
- Cannot all be seen, felt or smelt
- Can measure where most deposit



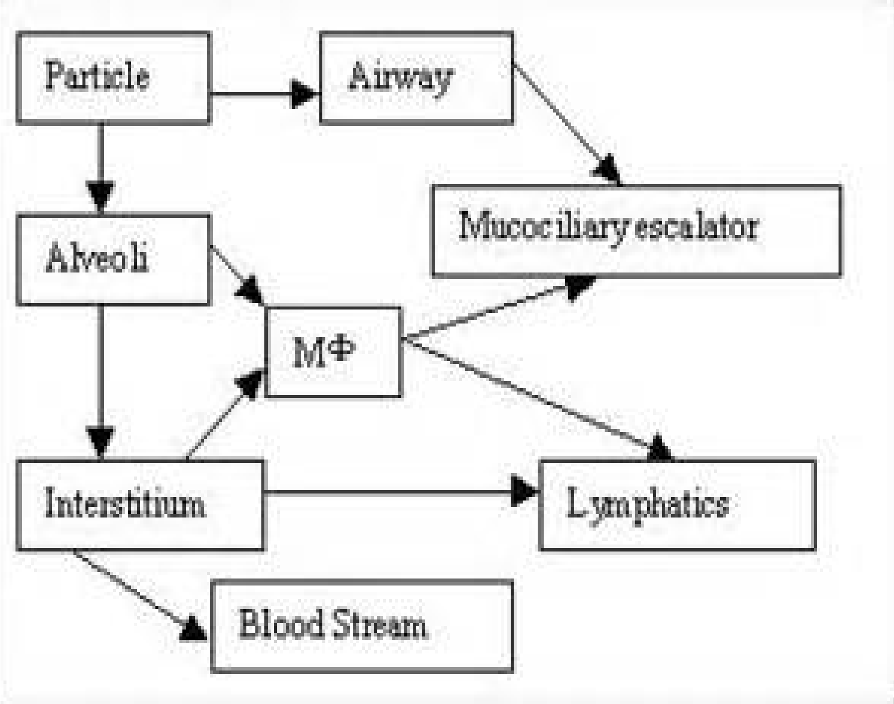

Normally

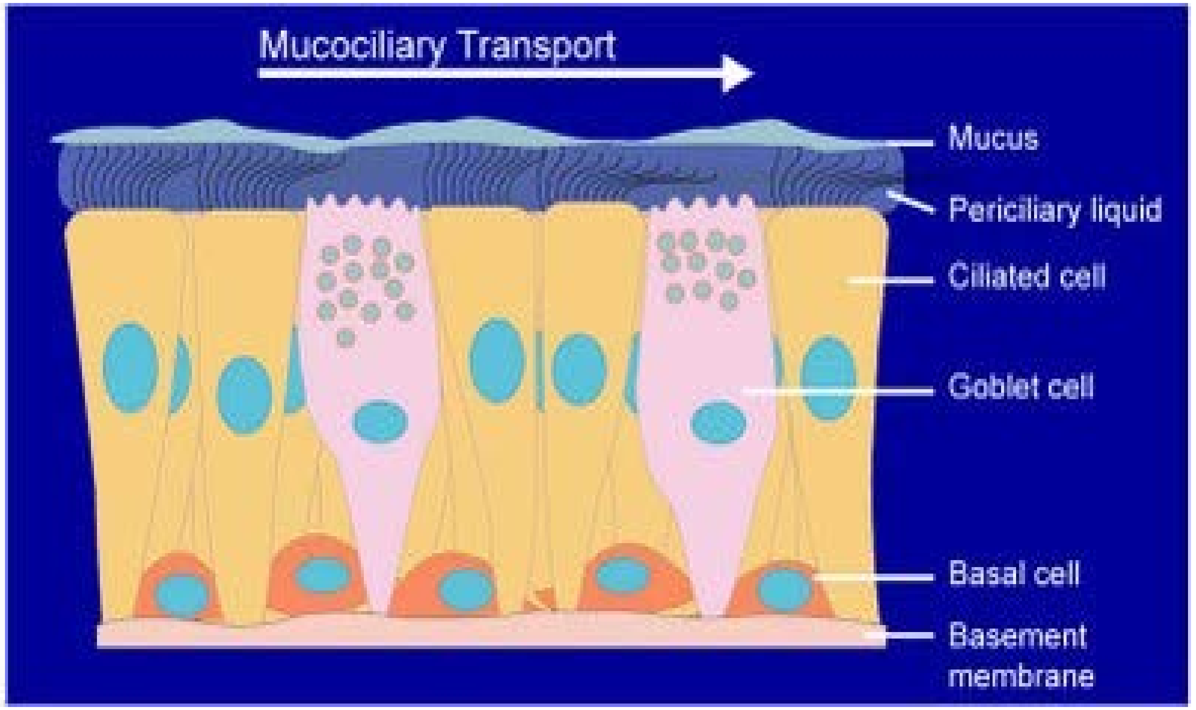
- Large particles deposit in nose
- Medium size particles deposit in trachea and bronchi
- Smaller particles deposit in lungs
- Clearing of particles from lungs occurs from the moment of impaction
- Lung defence cell involved = macrophage (big eater)
- Disease occurs when the defence mechanisms are overwhelmed, and may take many years to manifest itself.



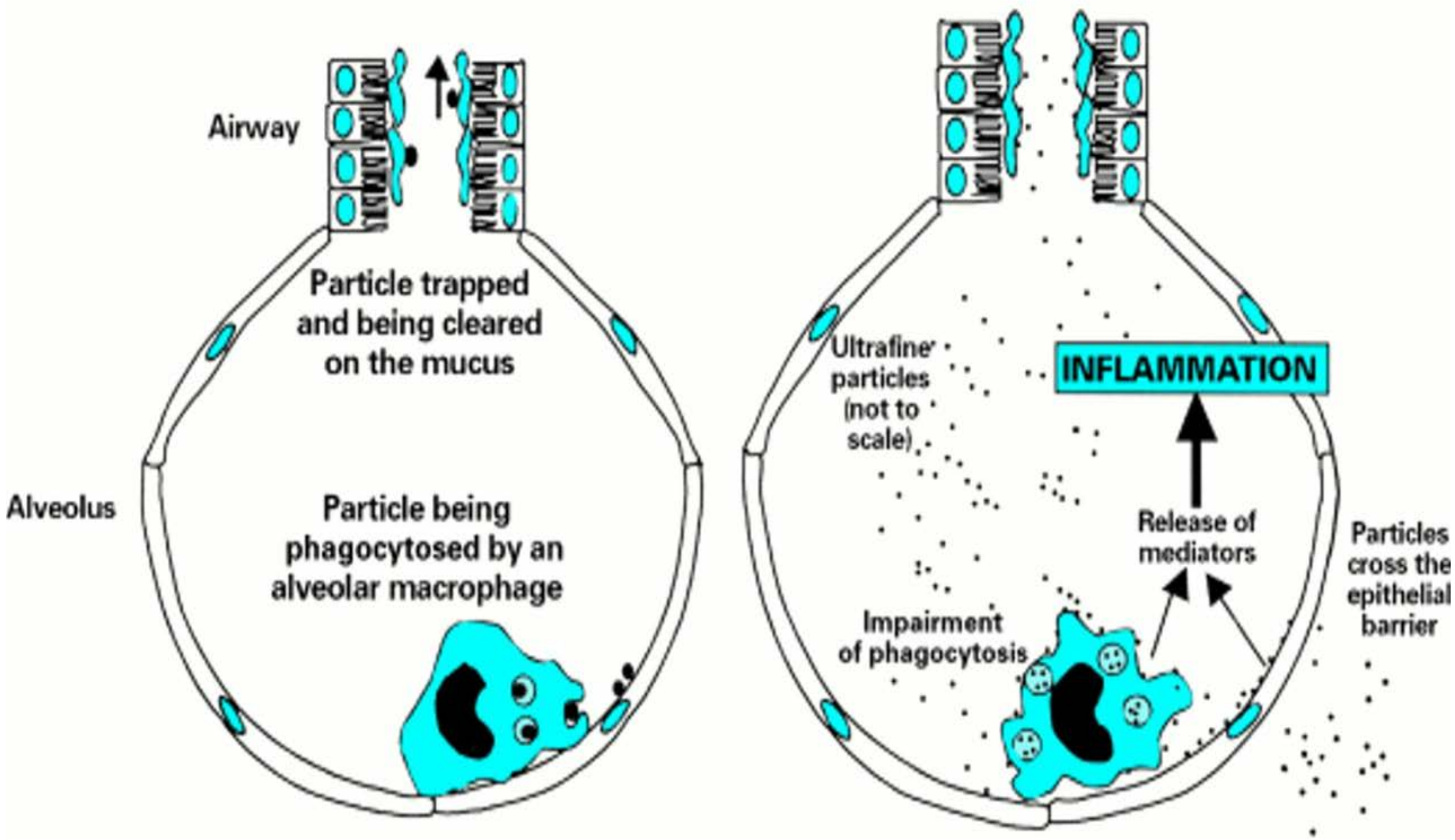


Mechanisms of lung clearance: most particles trapped and removed by your personal internal lung escalator



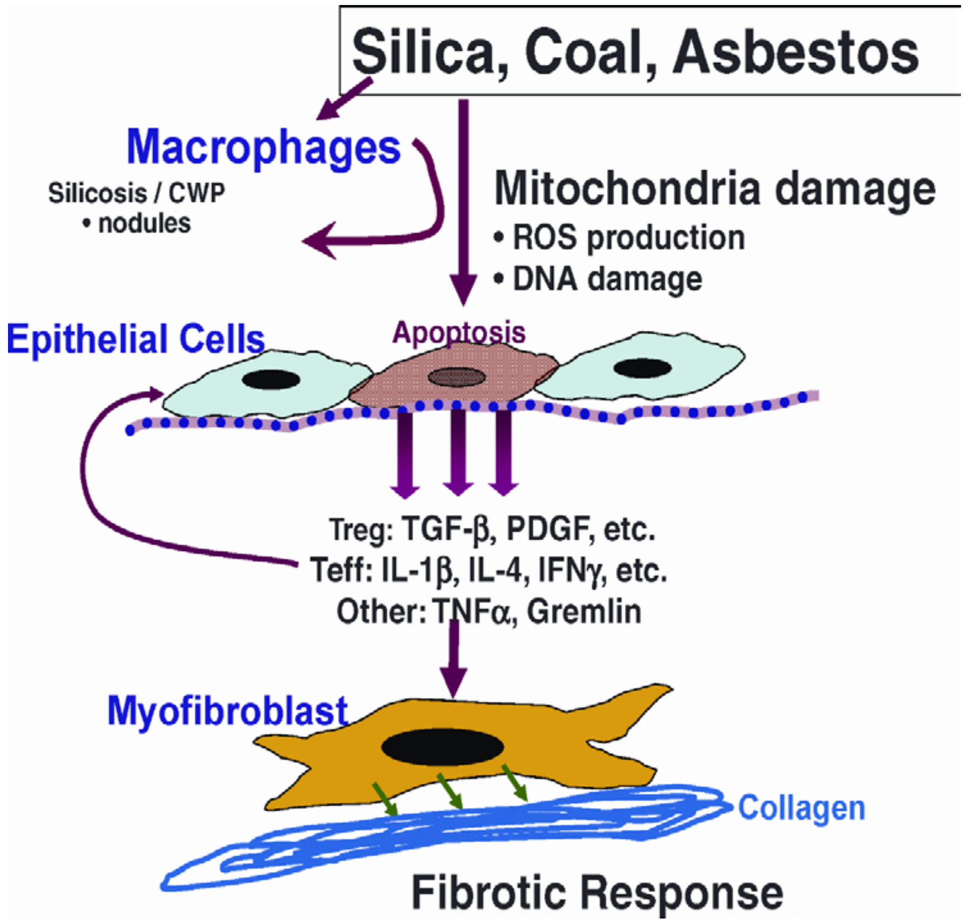


Dust particles reaching the alveolus



Dust exposure, dust retention and radiographic change: mechanisms

- Dust inhalation releases mediators
- Particles cause “oxidative stress” plays a role
- Genetic susceptibility likely important
- Inherent capability of lungs to clear dust is good; significant redundancy within lung
- Fibrosis results from long term dust inhalation



Pneumoconiosis research post-WWII: many treatments tried

- Post war mass X ray screening in south Wales
- Large epidemiological studies into coal workers pneumoconiosis laid the foundations of modern evidence-based medicine
- Many agents were tried for silicosis after beneficial effects found in animal studies e.g. inhaled aluminium, surface coating compounds e.g. polyvinyl-pyridine-N-oxide, anti-fibrotic agents e.g. beta amino proprionitrile (BAPN)
- Corticosteroids evaluated

- **However, no effective treatments were found**

ALUMINIUM POWDER INHALATIONS IN THE TREATMENT OF SILICOSIS OF POTTERY WORKERS AND PNEUMOCONIOSIS OF COAL-MINERS

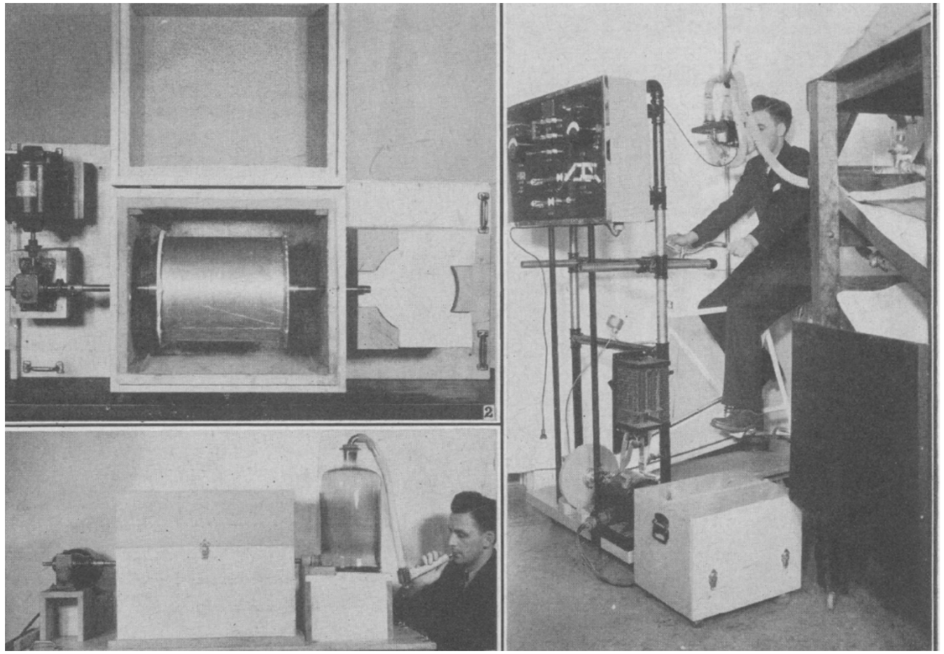
BY

M. C. S. KENNEDY

From the Medical Research Council Treatment Centre, North Staffordshire Royal Infirmary, Stoke-on-Trent

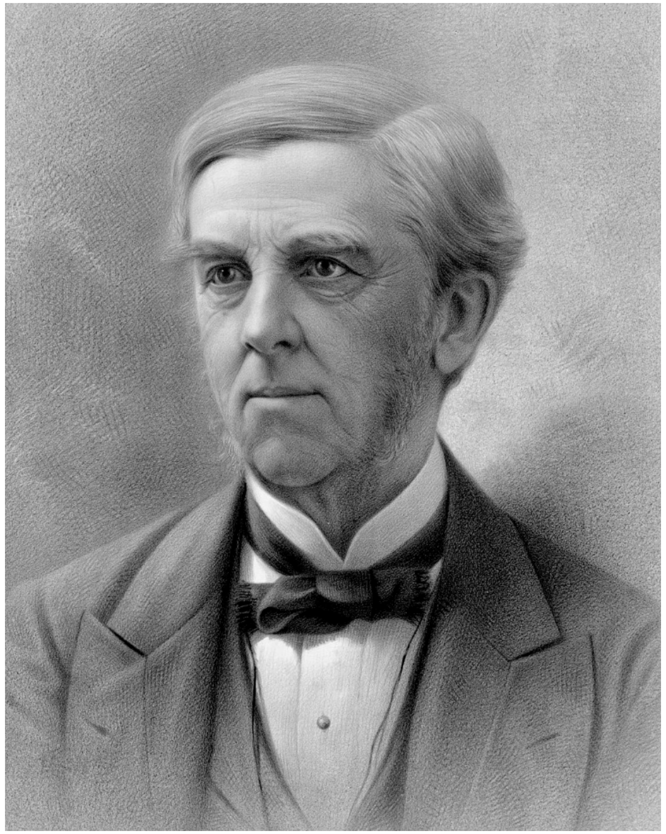
(RECEIVED FOR PUBLICATION DECEMBER 7, 1955)

Haldane in 1918 postulated the theory that the dust of certain mineral rocks had an antidotal effect on the fibrogenic action of siliceous dusts, a theory which has since been put to the test by animal investigators. Kettle in 1932 showed that iron-coated particles of quartz were inert when injected subcutaneously into animals, whereas uncoated quartz caused marked necrosis and cellular change in the subcutaneous tissues. In 1937 Denny, Robson and Irwin found that small quantities of metallic aluminium inhibited the solubility of siliceous material in the beaker, and that quartz particles coated with aluminium failed to produce fibrosis in the lungs of rabbits, whereas particles not so development of silicosis, or that it caused regression of the established disease. They recommended that carefully planned and controlled investigations be made into the value of this treatment. This recommendation was endorsed by the Aluminium Sub-committee of the Industrial Pulmonary Diseases Committee, and the present report gives an account of the investigation that was carried out in the Stoke-on-Trent area to evaluate the merits of aluminium inhalations for the treatment of established silicosis of pottery workers and pneumoconiosis of coal-miners. The object was to compare the relative efficacy of aluminium inhalations given in two very different doses (one of which was so



Resulted in therapeutic nihilism:

the contention that it is impossible to cure people or societies of their ills through treatment.



Oliver Wendell Holmes

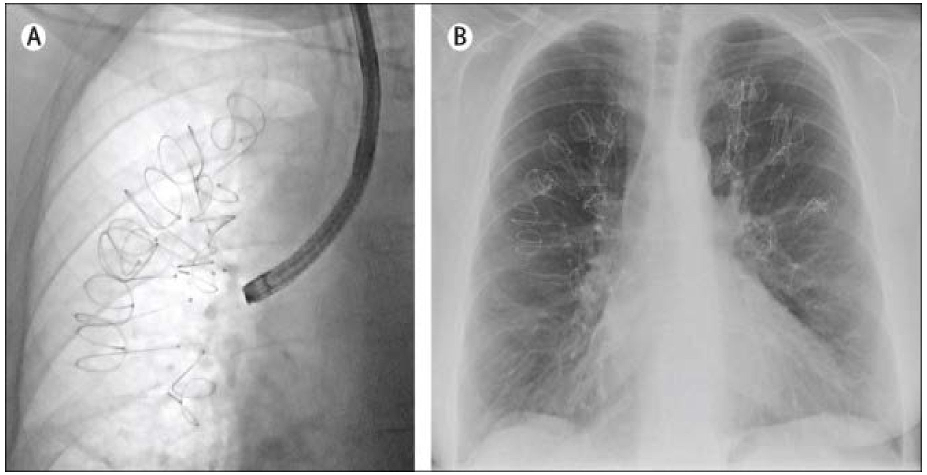
"...if the whole *materia medica*, as now used, could be sunk to the bottom of the sea, it would be so much the better for mankind – and all the worse for the fishes."

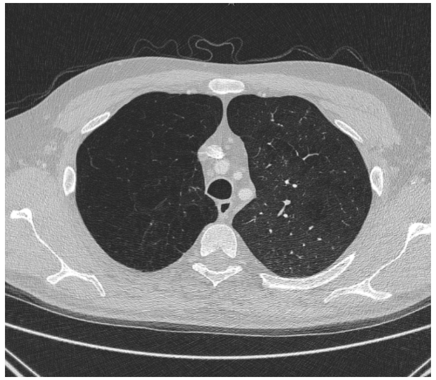
Ivan Illich: “modern medicine is a negation of health …. . it makes more people sick than it heals”.

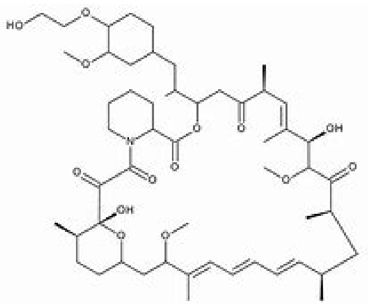
Especially after the demonstration of the adverse effects of smoking……

But…..many recent advances in treating respiratory diseases

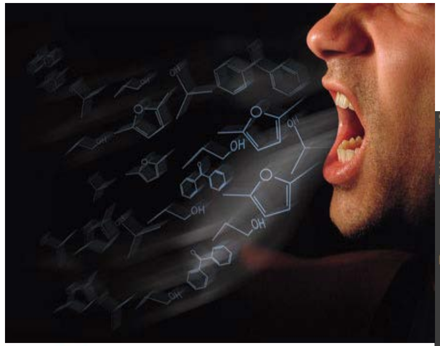
- Better imaging and diagnostic techniques
- Better anti-infective agents
- Targeted treatments for asthma, lung cancer, immune- mediated diseases, genetic disorders
- Improved surgical techniques with fewer complications; better bronchoscopic techniques
- Improved prevention (incl screening)
- Better understanding of genetic disorders
- Multi-disciplinary team care
- Move to a global respiratory community
- Vast change in data analysis; big data; robots
- More to come!

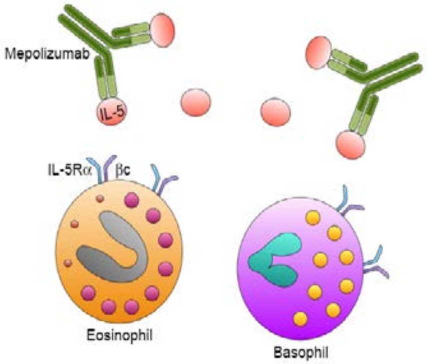


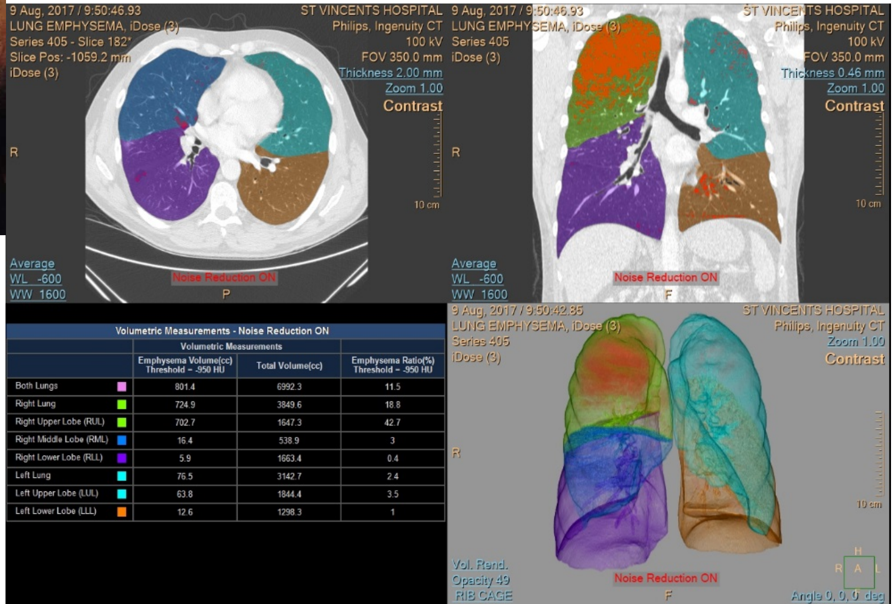




Everolimus (Afinitor, Novartis); $C_{53}H_{83}NO_{14}$; MW = 958







Volumetric Measurements - Noise Reduction ON			
	Volumetric Measurements		
	Emphysema Volume(cc) Threshold = -950 HU	Total Volume(cc)	Emphysema Ratio(%) Threshold = -950 HU
Both Lungs	801.4	6992.3	11.5
Right Lung	724.9	3849.6	18.8
Right Upper Lobe (RUL)	702.7	1647.3	42.7
Right Middle Lobe (RML)	16.4	538.9	3
Right Lower Lobe (RLL)	5.9	1663.4	0.4
Left Lung	76.5	3142.7	2.4
Left Upper Lobe (LUL)	63.8	1844.4	3.5
Left Lower Lobe (LLL)	12.6	1298.3	1

Treatments in general: the whole person

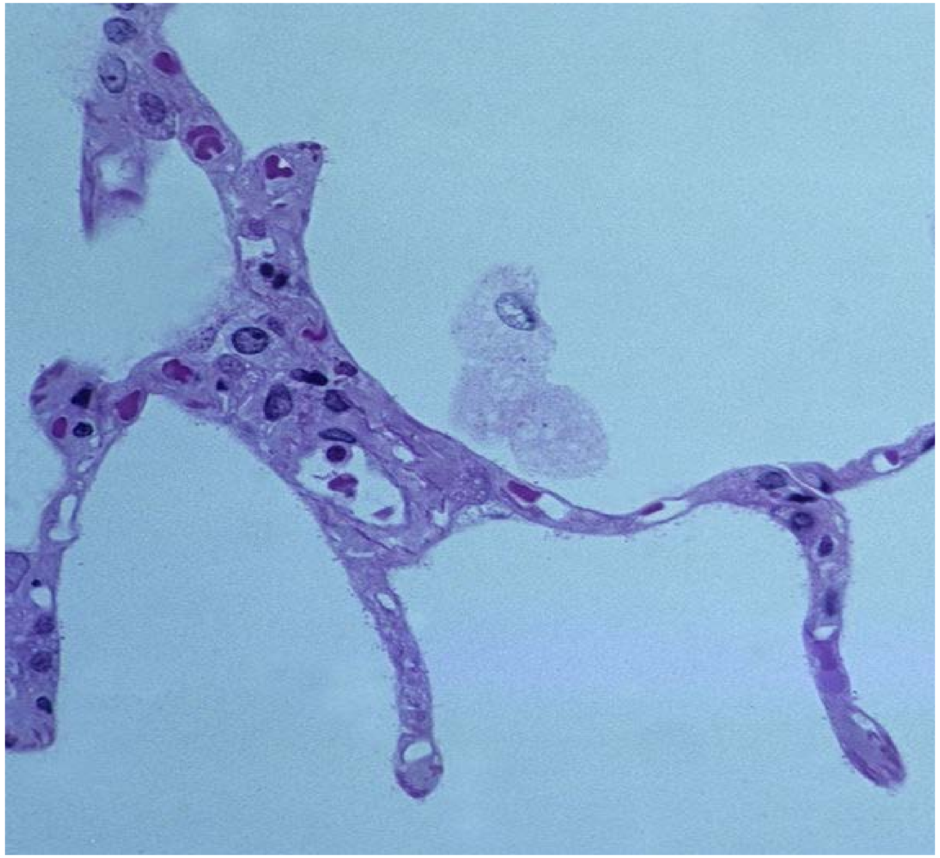
General assistance:

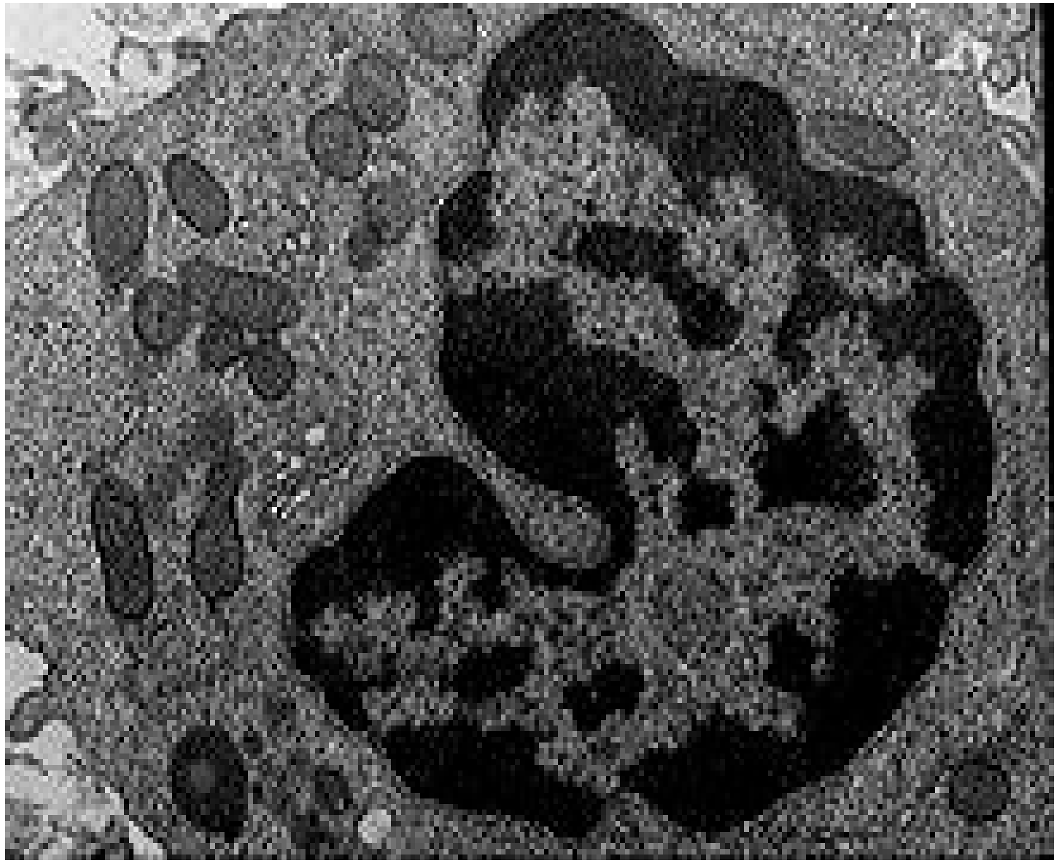
- Smoking, vaping and drug use reduction/cessation
- Vaccinations
- Weight loss & fitness training
- Diet
- Psychological support eg. for anxiety & depression
- Financial and compensation support
- Pulmonary rehabilitation

Treatment of other respiratory disorders: inhalers, antibiotics, biologicals, steroids etc

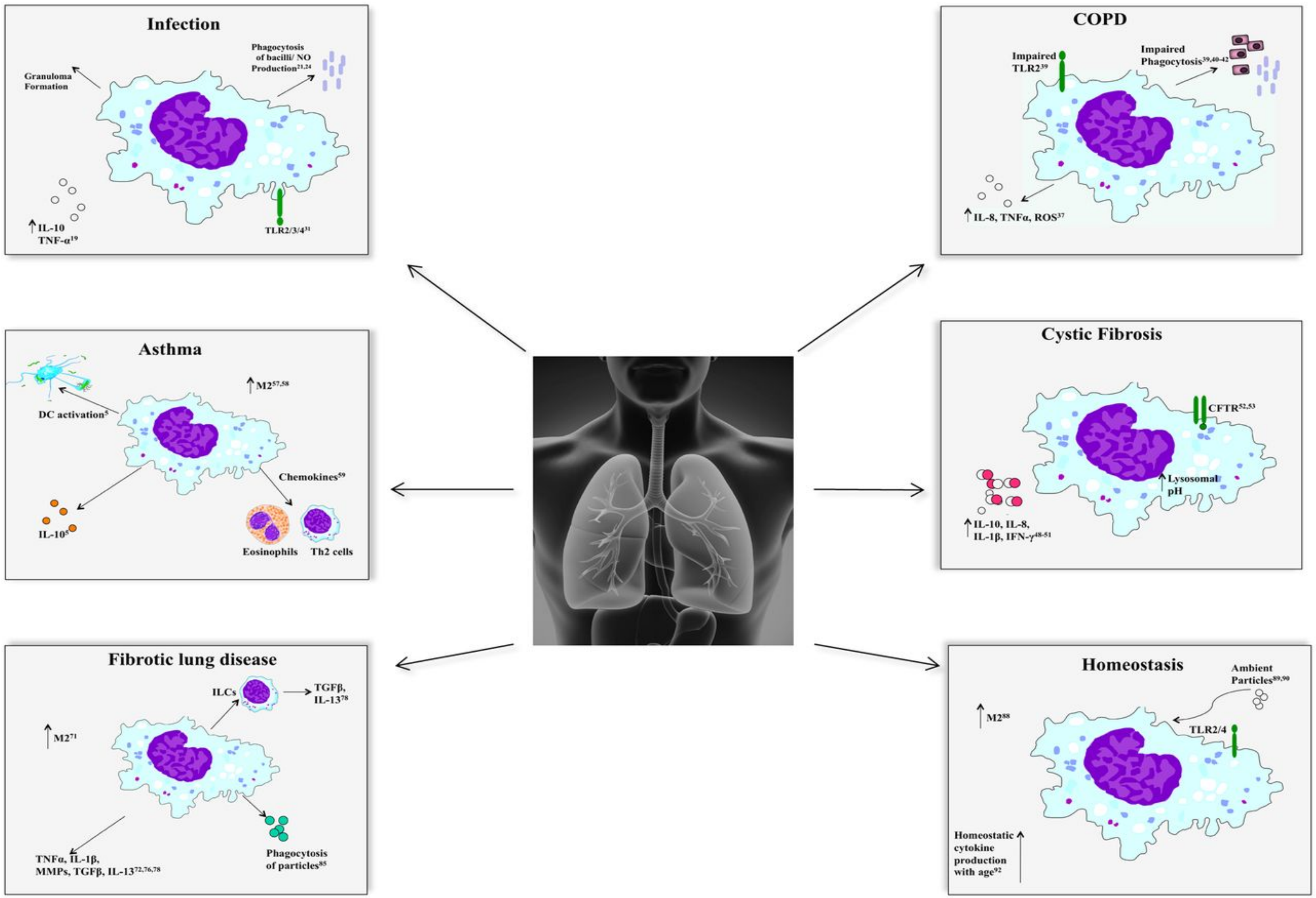
Dale M, Mckeough Z et al. (2015). Exercise training to improve exercise capacity and quality of life in people with non-malignant dust-related respiratory diseases. The Cochrane database of systematic reviews.

Learning to target specific pathways in particular diseases: the alveolar macrophage: long known to be a key player in coal workers’ pneumoconiosis





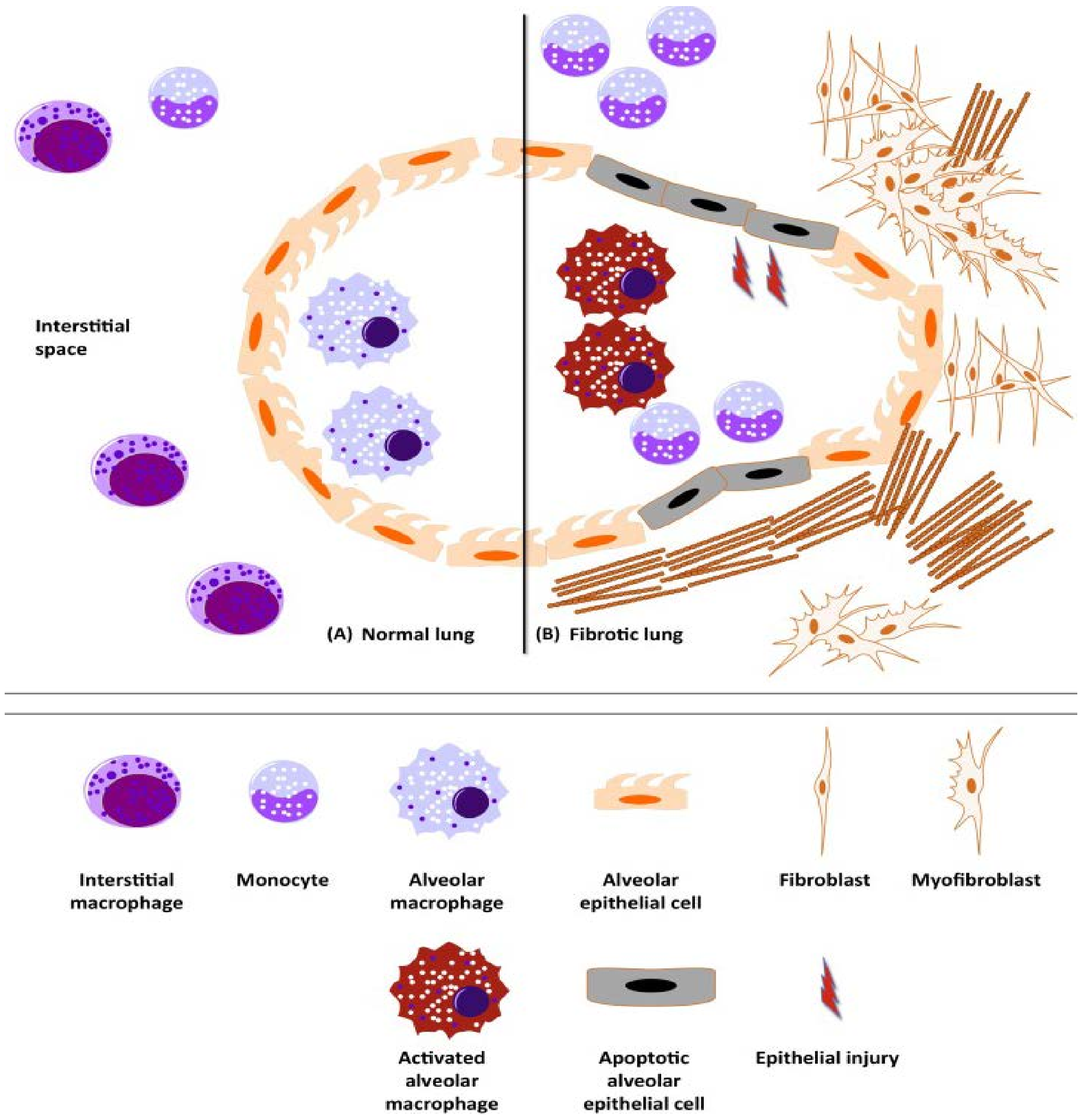
We know that pulmonary macrophages play a central role in many different lung diseases



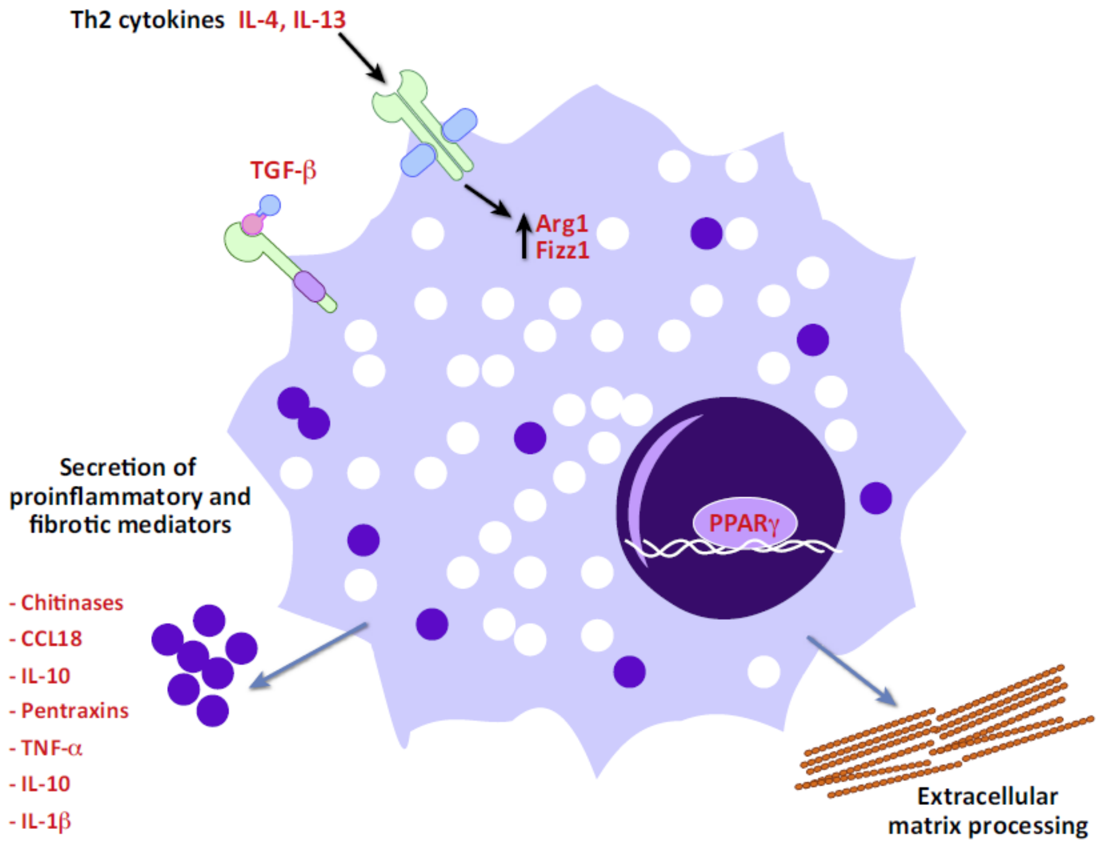
Adam J Byrne et al. Thorax 2015;70:1189-1196

THORAX

Role of the alveolar macrophage in pulmonary fibrosis



Macrophage-derived molecular targets for treatment of interstitial lung disease



Abbreviations: Arg, arginase; FIZZ, found in inflammatory zone; GM-CSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; IRF, interferon regulatory factor; PPARg, peroxisome proliferator activated receptor g; TGF, transforming growth factor; TNF, tumour necrosis factor.

Insights from other lung diseases

Idiopathic Pulmonary Fibrosis (IPF), is a rare serious condition that affects the fragile tissue in the lungs

Normal healthy lung tissue is soft and flexible, allowing easy breathing

In IPF, the lung tissue is damaged, becoming scarred over time. This process is called fibrosis

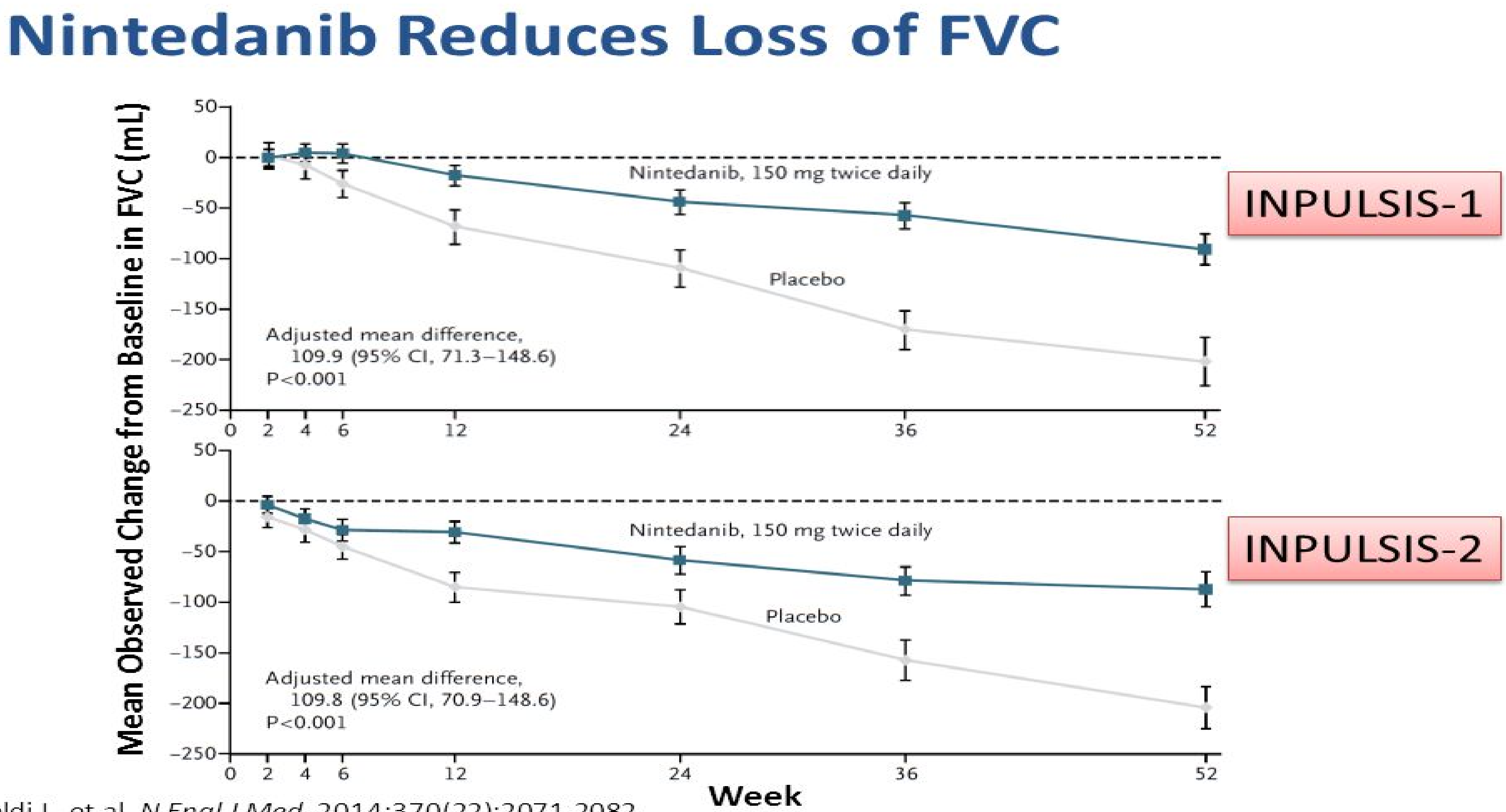
As IPF gets worse, scarring spreads through the lungs which makes breathing more difficult. Once the lung tissue is damaged from progressive scarring, unfortunately it doesn't recover

Antifibrotic agents currently available in Australia:

Nintedanib (Boehringer Ingelheim)

Perfenidone (Roche)

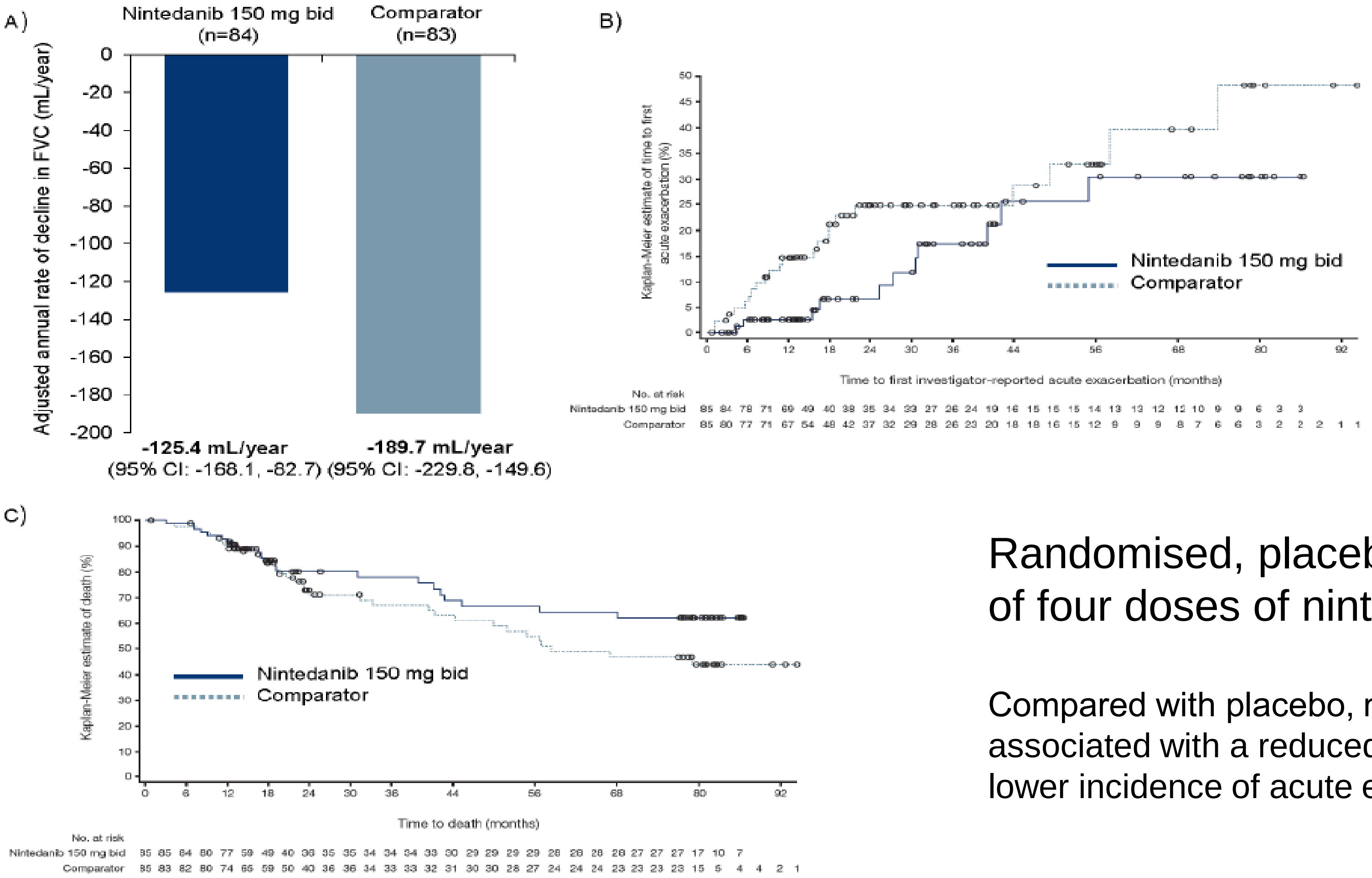
New treatments for IPF: nintedanib
INPULSIS Trials



Richeldi L, et al. *N Engl J Med.* 2014;370(22):2071-2082.

Nintedanib: The TOMORROW Trial

Richeldi L, Kreuter M, Selman M, et al
Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension
Thorax 2018;73:581-583.



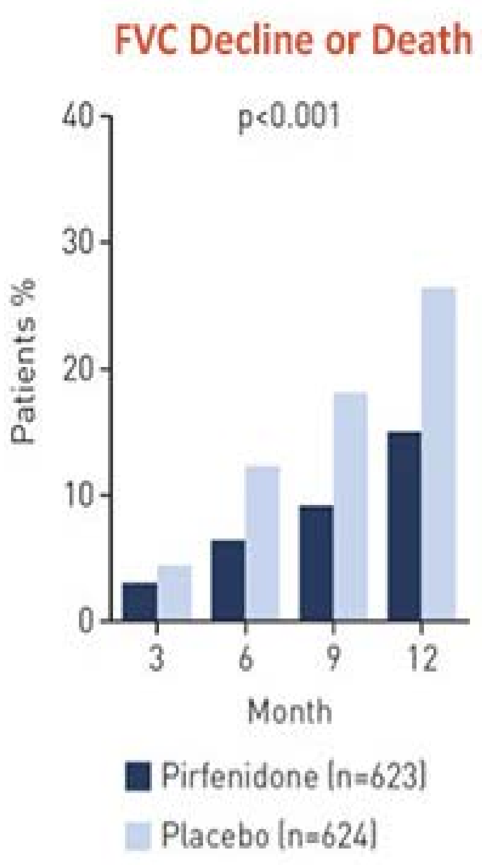
Randomised, placebo-controlled, 52-week trial of four doses of nintedanib in IPF.

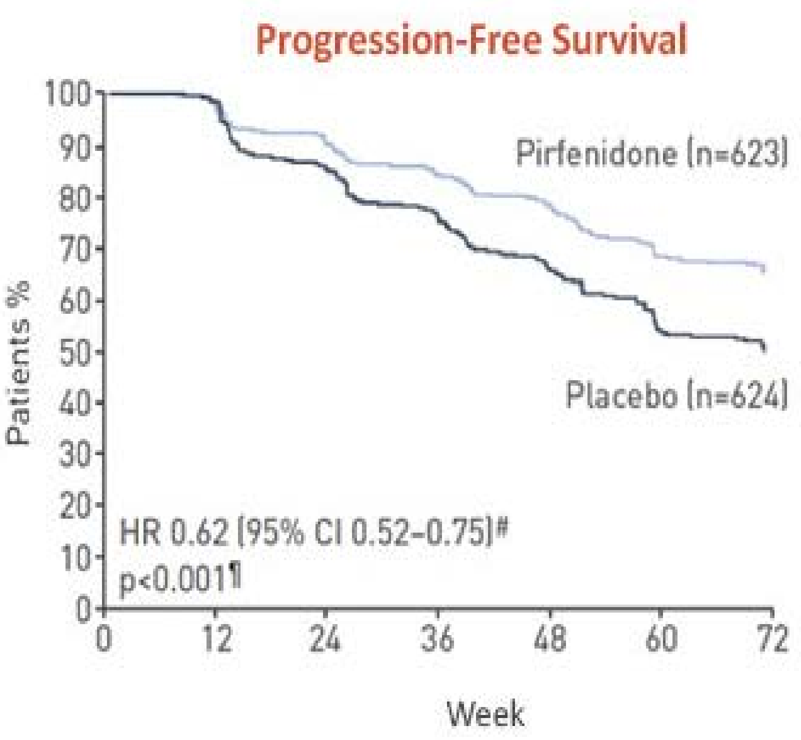
Compared with placebo, nintedanib 150 mg twice daily was associated with a reduced annual rate of decline in FVC and a lower incidence of acute exacerbations.

Pirfenidone in patients with idiopathic pulmonary fibrosis:

CAPACITY and ASCEND trials

Noble PW, Albera C, Bradford WZ, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J*. 2016;47(1):243-253 .





N=1,247 patients

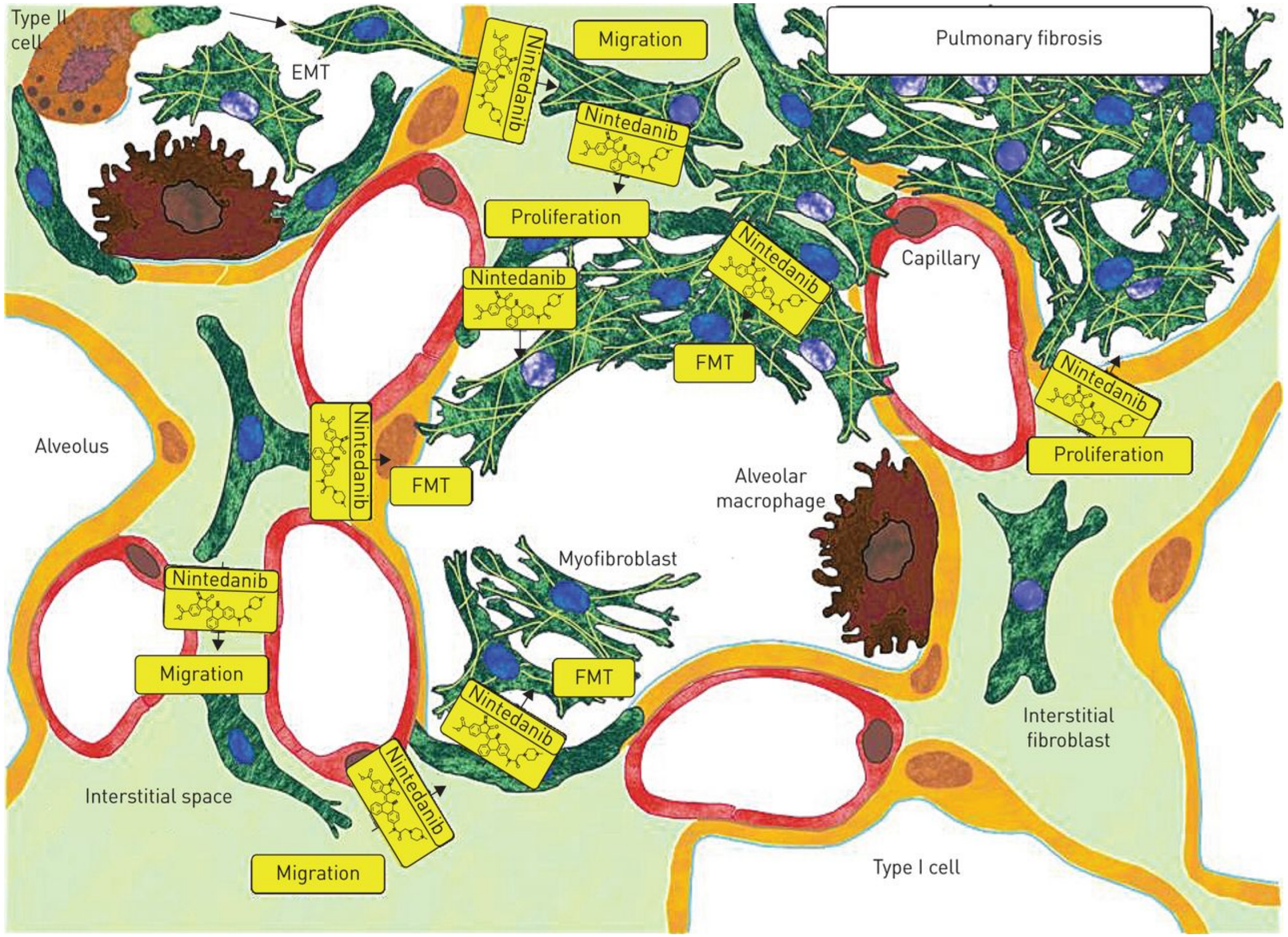
At 1 year, pirfenidone reduced the proportion of patients with a ≥ 10% decline in percent predicted forced vital capacity or death by 43.8% (95% CI 29.3–55.4%, left figure)

Also increased the proportion of patients with no decline by 59.3% (95% CI 29.0–96.8%).

Treatment benefit was also observed for progression-free survival, as 6-minute walk distance and breathlessness.

Gastrointestinal and skin-related adverse more common in the pirfenidone group, but rarely led to discontinuation.

Current understanding of the mode of action of nintedanib in fibrotic lung diseases: mulitiple pathways blocked.



Lutz Wollin et al. Eur Respir J
doi:10.1183/09031936.00174914

Nintedanib in Progressive Pneumoconiosis Study (NIPPs)

Trial design: NiPPS

Patient referred to investigators in Sydney and key regional sites (clinical, advocacy groups, surveillance programs)

Clinical investigations: standardised occupational history, HRCT (standardised technique; include lung emphysema software and IF software), full lung function in dedicated laboratory, K-BILD questionnaire, review of biopsy & other information.

Occupational MDT (web-based access for distant sites)

Pneumoconiosis

Not pneumoconiosis

Enrol in NiPPS

Treat appropriately

Do not wish treatment

Monitor clinically with annual Ix as below

Nintedanib 150 mg PO BiD after informed consent

Study visits: baseline, every 2 weeks for 4 weeks then 6 weekly until 1 yr; 6 monthly thereafter and including end of study visit 4-12 weeks after study cessation.

K-BILD at each visit; 6 min walk test every 3 months for first year. Liver function tests etc as per clinical protocol.

Annual full lung function in respiratory laboratory

Annual HRCT

Annual 6 min walk

36 months: End of study: assess efficacy; assess feasibility of larger study; continue therapy in those in whom beneficial effect demonstrated.

- Open label trial of nintedanib 150 mg BD in 100 patients with pneumoconiosis (silicosis, diffuse dust fibrosis, coal workers pneumoconiosis, asbestosis)
- Stratified by severity
- Assessment by: questionnaires, 6 min walk, lung function (including DLCO), HRCT
- Prospective evaluation of acute exacerbation rates & LRTIs
- 3 year trial
- Funded as investigator-initiated trial by Boehringer-Ingelheim

Can washing out the lung work? Whole lung lavage (WLL) in pneumoconiosis

WLL can reduce lung dust burden in pneumoconiosis by whole-lung lavage. Wilt JL, Banks DE, Weissman DN et al. .Occup Environ Med. 1996 Jun;38(6):619-24.

Two coal miners with ILO category 2 opacities treated with WLL

Cell Type	Subject 1		Subject 2	
	Right Lung	Left Lung	Right Lung	Left Lung
Total Cells ($\times 10^6$)	5.24	3.45	7.49	9.78
Macrophages (%)	88	94	46	69
Lymphocytes (%)	6	3	4	13
Neutrophils (%)	3	2	51	16
Eosinophils (%)	2	2	1	1

TABLE 1. Cell Recovery and Differential Counts

Estimates of enzymes, cytokines, and growth factors removed from the workers' lungs by WLL are presented in Table 2. The proinflammatory cytokines IL-1[beta] and IL-6 were elevated in the lavage fluid from both subjects, but especially in Subject 2. TNF-[alpha] was reduced except in the lavage fluid from the right lung of Subject 2. The concentrations of antioxidant enzymes (GSHP and SOD), usually associated with protection of the lungs from injury, were elevated in both subjects.

Cytokine/Enzyme	Expected*	Subject 1		Subject 2	
		Right	Left	Right	Left
Interleukin 1-β (pg/mL)	23.2 ± 8.0	41	37	209	189
Interleukin 6 (pg/mL)	4.7 ± 1.2	144	86	225	22
Tumor Necrosis Factor-α (pg/mL)	23.3 ± 7.1	8.3	5.9	105	4.9
Transforming Growth Factor β-$_1$ (ng/mL)	.07 ± .03	.28	0	.19	.16
Transforming Growth Factor β-$_2$ (pg/mL)	52.7 ± 19.9	169	134	200	52
Superoxide Dismutase (ng/mL)	8.7 ± 2.5	38	36	41	46
Glutathione Peroxidase (U/mL)	18.4 ± 4.3	149	118	211	137
Alpha-1-Antitrypsin (mg/mL)	5.6 ± 1.2	179	117	420	9

* Values obtained from bronchoalveolar lavage on 19 non-miner control subjects in our laboratory (Weber SL, et al. Role of cytokines and mineral particle profile in the development of coal workers' pneumoconiosis as assessed by bronchoalveolar lavage. *Appl Occup Environ Hyg*. In press.

Comparing the therapeutic effect of lung transplantation with the therapeutic effect of whole lung lavage for the patients with end-stage pneumoconiosis.

Mao WJ, Zhang YM, Chen JY et al. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2011 Oct;29(10):746-50. Thoracic Surgery, Nanjing University

Small study of 17 patients; compared effects of WLL with LTx in end-stage pneumoconiosis

- Between June 2002-Feb 2011, 5 cases had single LTx and 12 WLL.
- LTX group: clinical symptoms, lung function and blood gas indicators were improved, pulmonary artery pressures decreased to normal levels, chest imaging showed that implanted lung was with clear lung markings but other lung showed progression
- WLL group: clinical symptoms improved in the 6 months after treatment but declined with time. Lung function in 6 months improved but decreased after 2 years, pulmonary artery hypertension worsened. Disease progression in the chest imaging examination was not found in 6 months WLL, but appeared in 1 - 2 years after WLL.
- **Conclusions:**
  - Survival: LTx - 41 months; WLL - 22.4 months
  - LTx has greater risk of death in the peri-operative period, but patients after LTx may have long survival times with good quality of life.
  - Clinical symptoms and lung function of patients can be improved temporarily after WLL, but survival time of WLL is inferior to that of LTx.
  - Significant complication rate with both treatments

Other treatments: e.g. new biological agents

Treating pulmonary silicosis by blocking interleukin 1.

Cavalli G, Fallanca F et al. Am J Respir Crit Care Med 2015; 191: 596-598

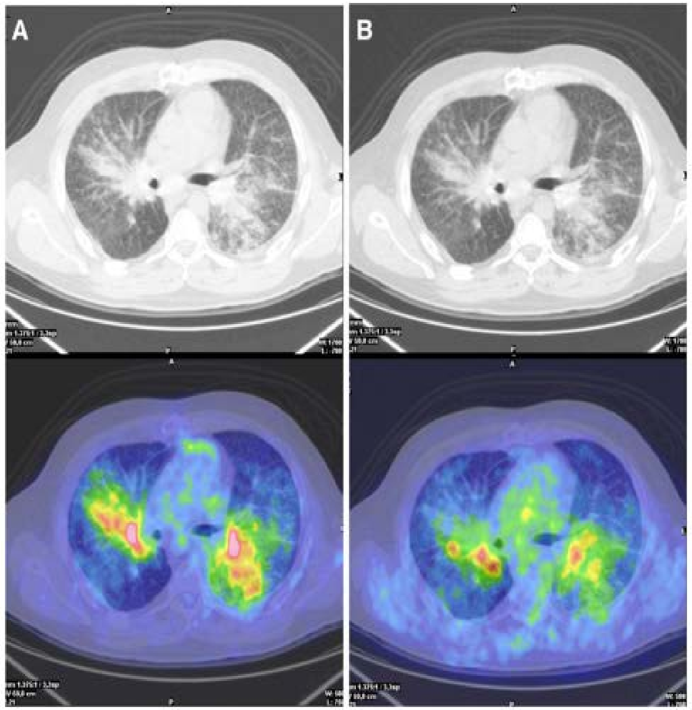


Figure 1. (*A*) On admission, chest computed tomography scan revealed bilateral ground-glass opacities. Positron emission tomography/computed tomography scan showed marked tracer uptake in the lungs bilaterally: standardized uptake value was 9.3 in the right lung and 8.5 in the left lung. (*B*) After 6 months of anakinra treatment, repeated positron emission tomography/computed tomography documented a marked decrease in the tracer uptake in both lungs. Standardized uptake value was 8.0 in the right lung and 5.9 in the left lung, with a standardized uptake value variation of −13% in the right lung and −31% in the left lung compared with baseline.

- 37 yr old miner
- Worked in marble cave for 7 years without precautions
- Presented with cough and breathlessness
- Silicosis diagnosed
- Treated with corticosteroids and antibiotics without response; p02 64 mmHg
- Treated with off label anakinra 100 mg s/c daily for 6 months
- Significant clinical, CT and PET improvement
- Oxygenation improved to 84 mmHg; DLCO improved; RFTs otherwise unchanged

Conclusions

- There are a variety of potential treatments for interstitial lung diseases now available. Coal workers' pneumoconiosis and silicosis are highly likely to be treatable, especially if identified in their early stages
- Treatments for other lung diseases are effective
- Pneumococcal and other vaccines are well documented to prevent infections which can cause disease progression
- Smoking (and vaping) are treatable habits and need to be addressed
- Pulmonary rehabilitation highly likely to be effective
- Therapeutic nihilism should be overcome!