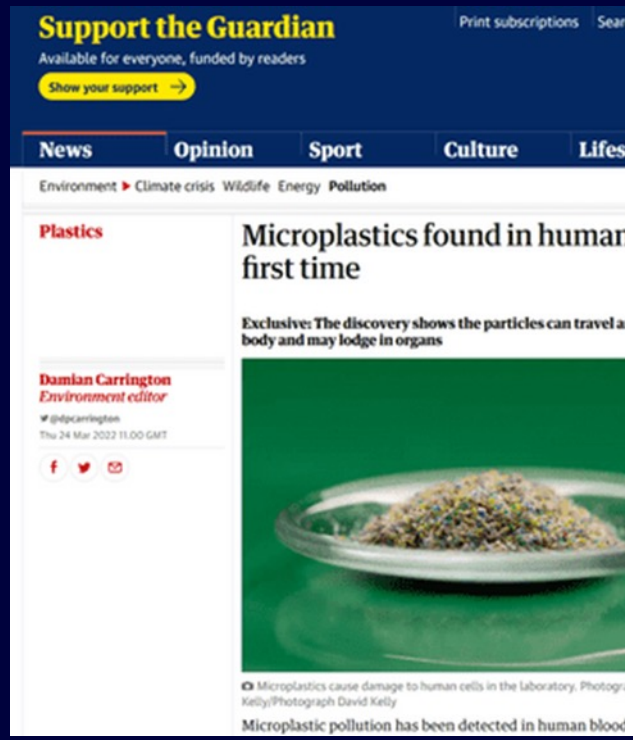
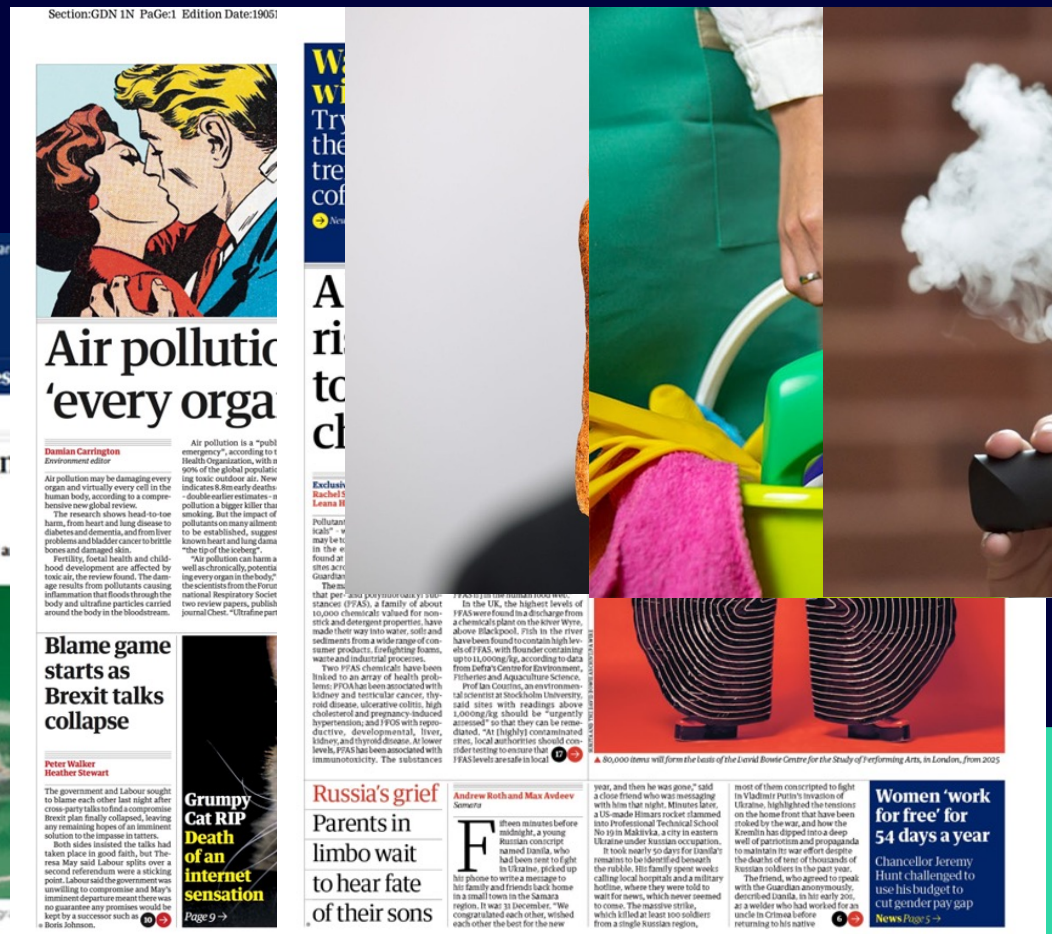
Lungs, Gut, and Skin: Biological Interfaces with the Outside World

Dr Ian Mudway



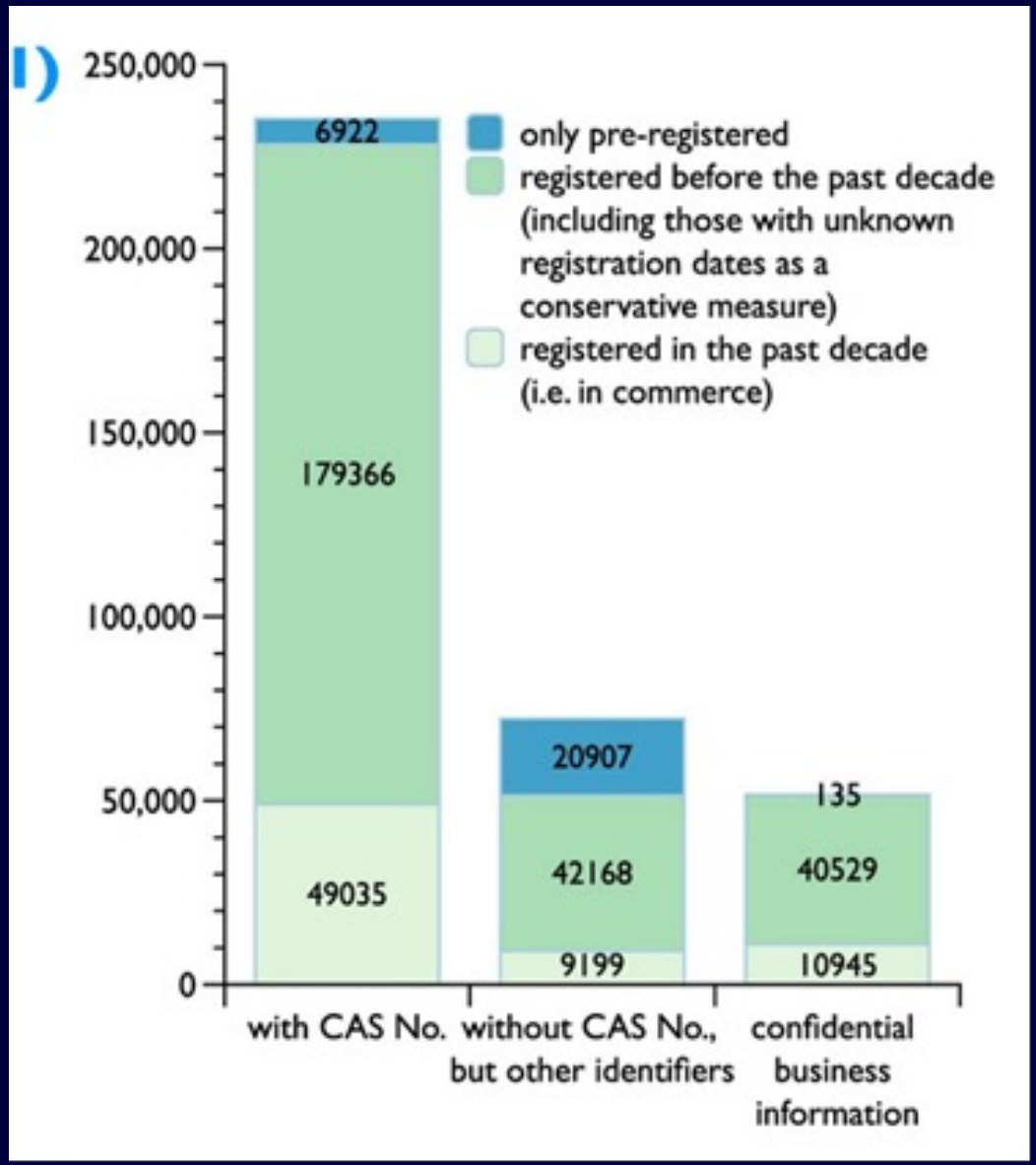


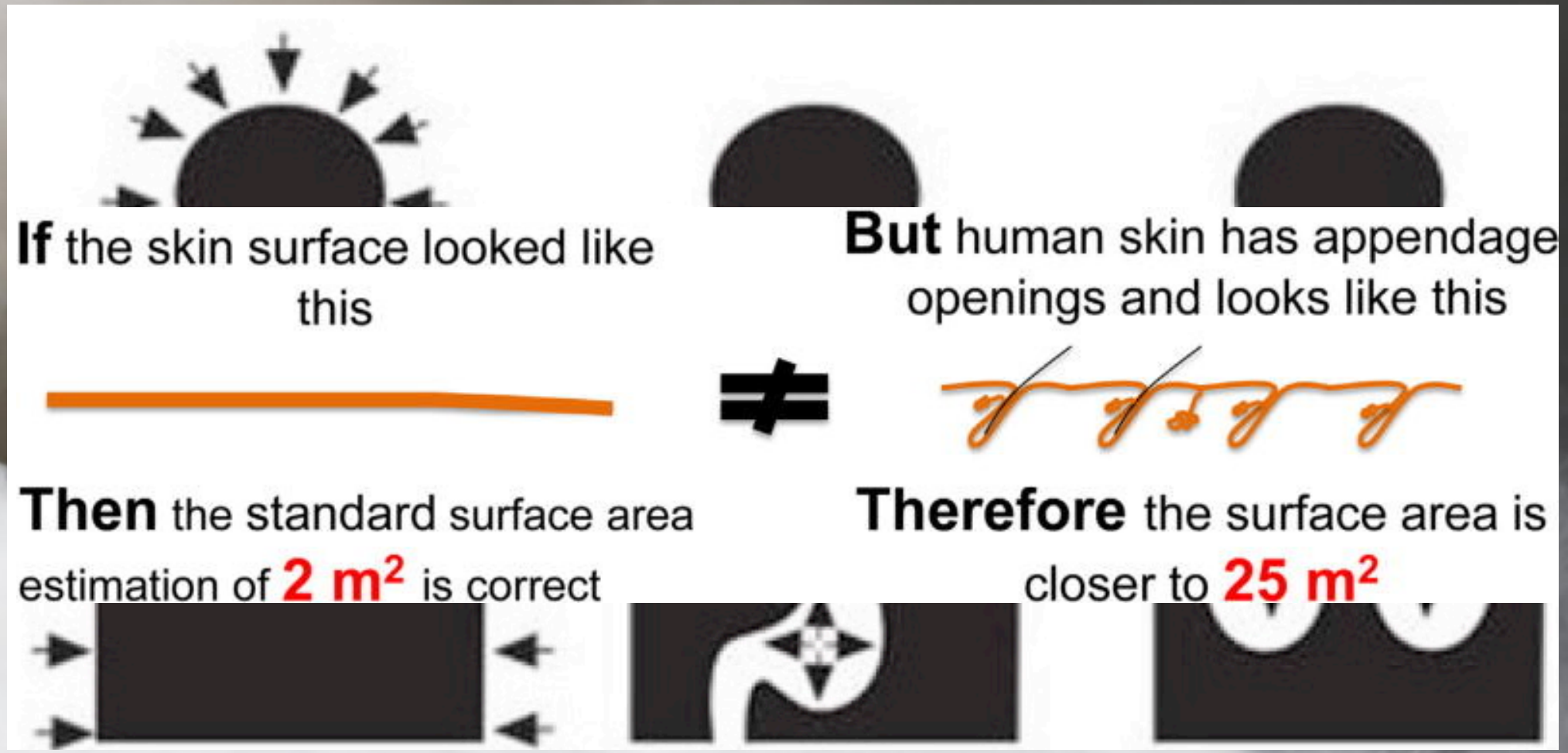
EST. 1597

GRESHAM COLLEGE

Chemical Complexities

- 201 million chemicals reported in the literature since early 1800s (CAS registry, as of today's date)
- Global inventory of chemicals licenced for manufacture and sale: 359,206 https://doi.org/10.1021/acs.est.9b06379, About 100,000 used in the EU https://echa.europa.eu/information-on-chemicals/ec-inventory
- REACH has 26,642 substances https://echa.europa.eu/information-on-chemicals/registered-substances





2 m^2

(Mosteller, 1987)

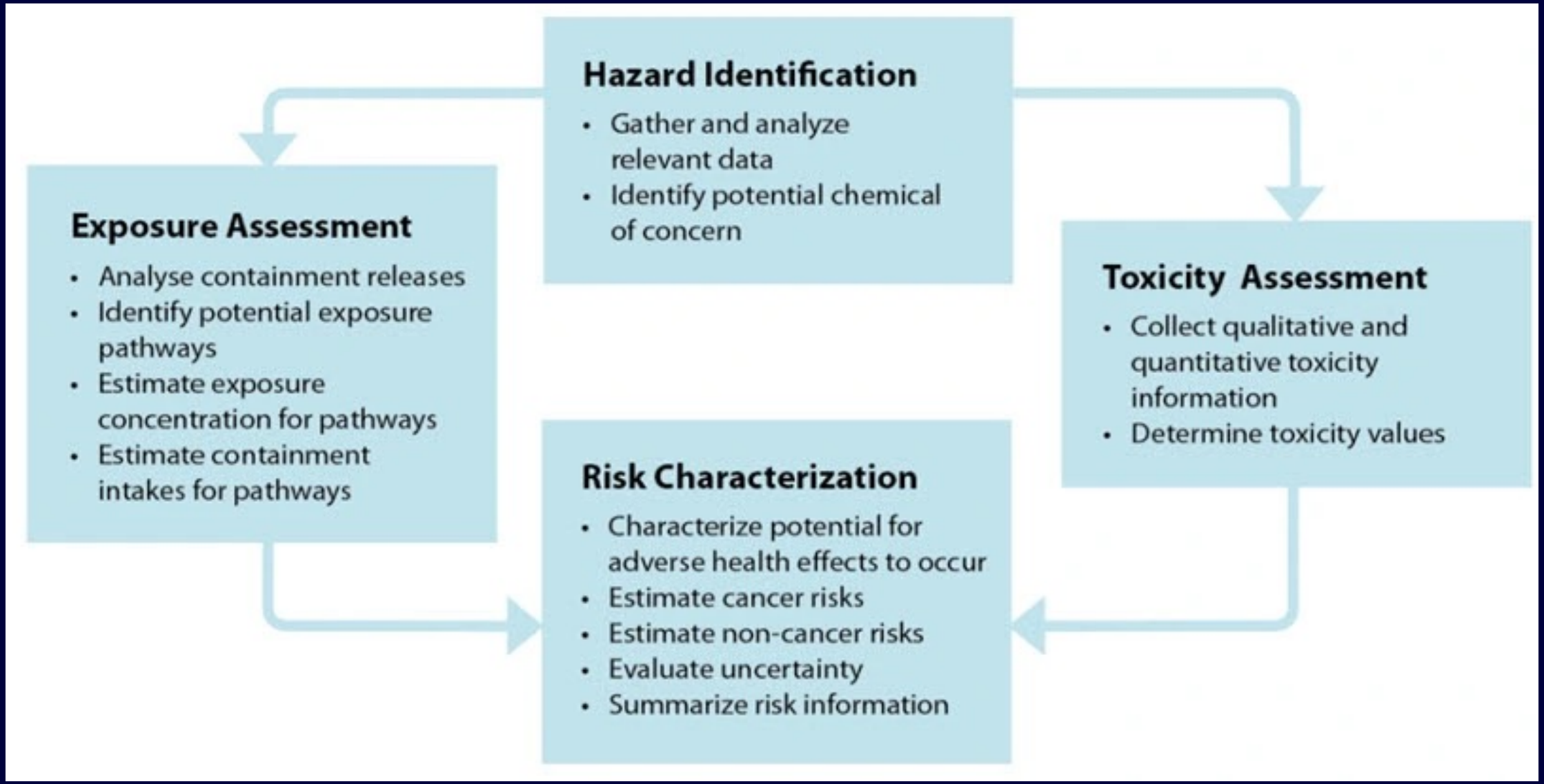
30 m^2

(Helander and Fandriks, 2014)

50-130 m^2

(Hasleton, 1972; Weibel, 2009)

Hazards & Risks


Hazard Identification
• Gather and analyze relevant data
• Identify potential chemical of concern
Exposure Assessment
• Analyse containment releases
• Identify potential exposure pathways
• Estimate exposure concentration for pathways
• Estimate containment intakes for pathways
Toxicity Assessment
• Collect qualitative and quantitative toxicity information
• Determine toxicity values
Risk Characterization
• Characterize potential for adverse health effects to occur
• Estimate cancer risks
• Estimate non-cancer risks
• Evaluate uncertainty
• Summarize risk information

Individual Susceptibility

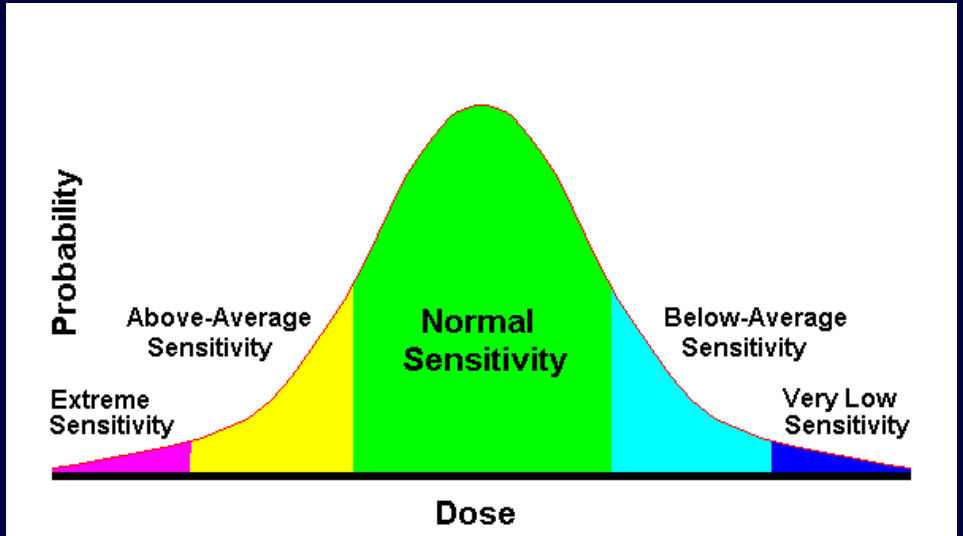
Gender

Age—young

- underdeveloped excretory mechanisms
- underdeveloped biotransformation enzymes
- Underdeveloped antioxidant systems
- underdeveloped blood-brain barrier
- Lung/brain (BBB) immaturity

Age—old

- changes in excretion and metabolism rates
- nutritional status
- depressed immunity
- diminished antioxidant defenses
- pre-existing health conditions
- Previous or Concurrent Exposures

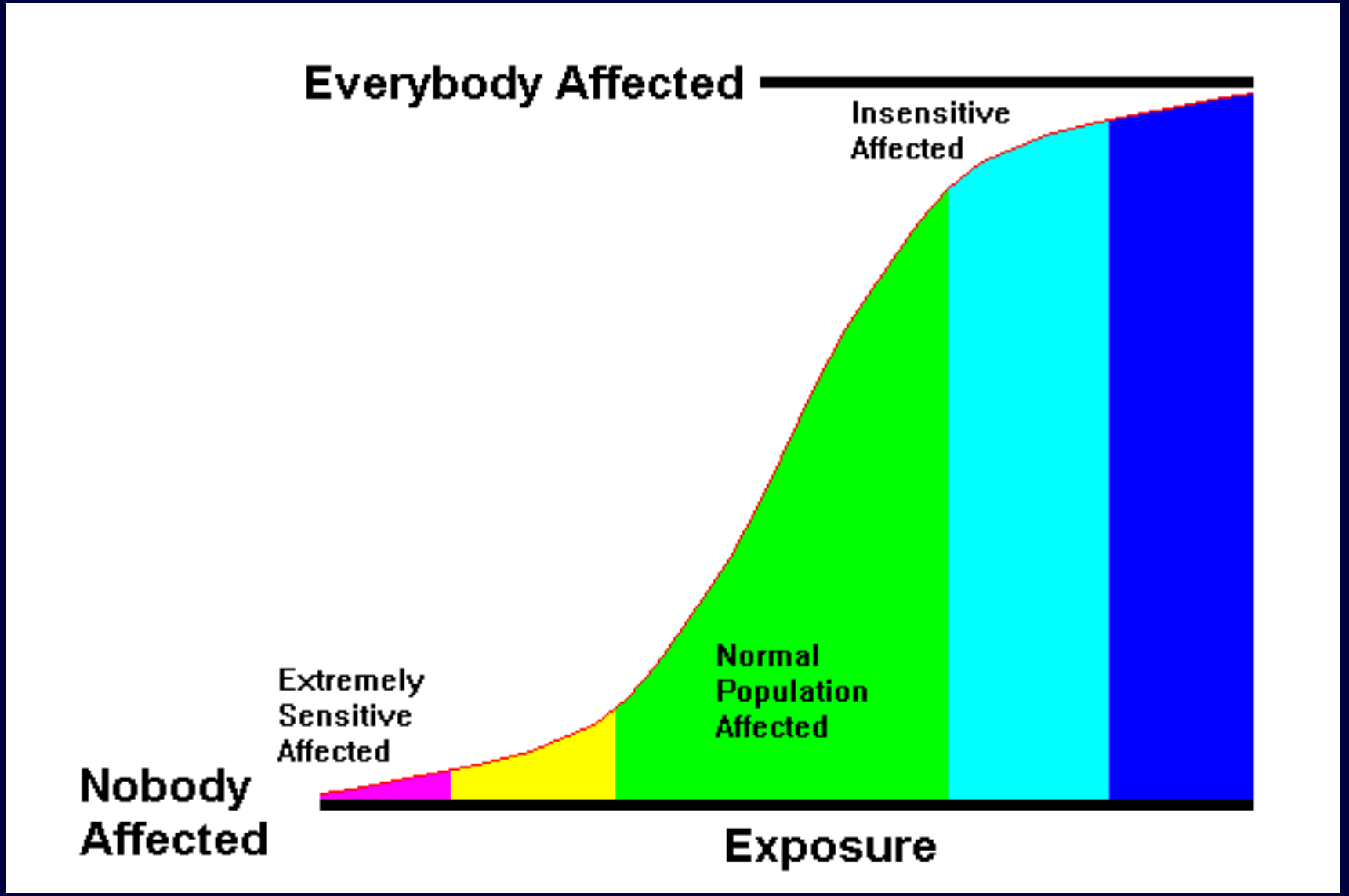


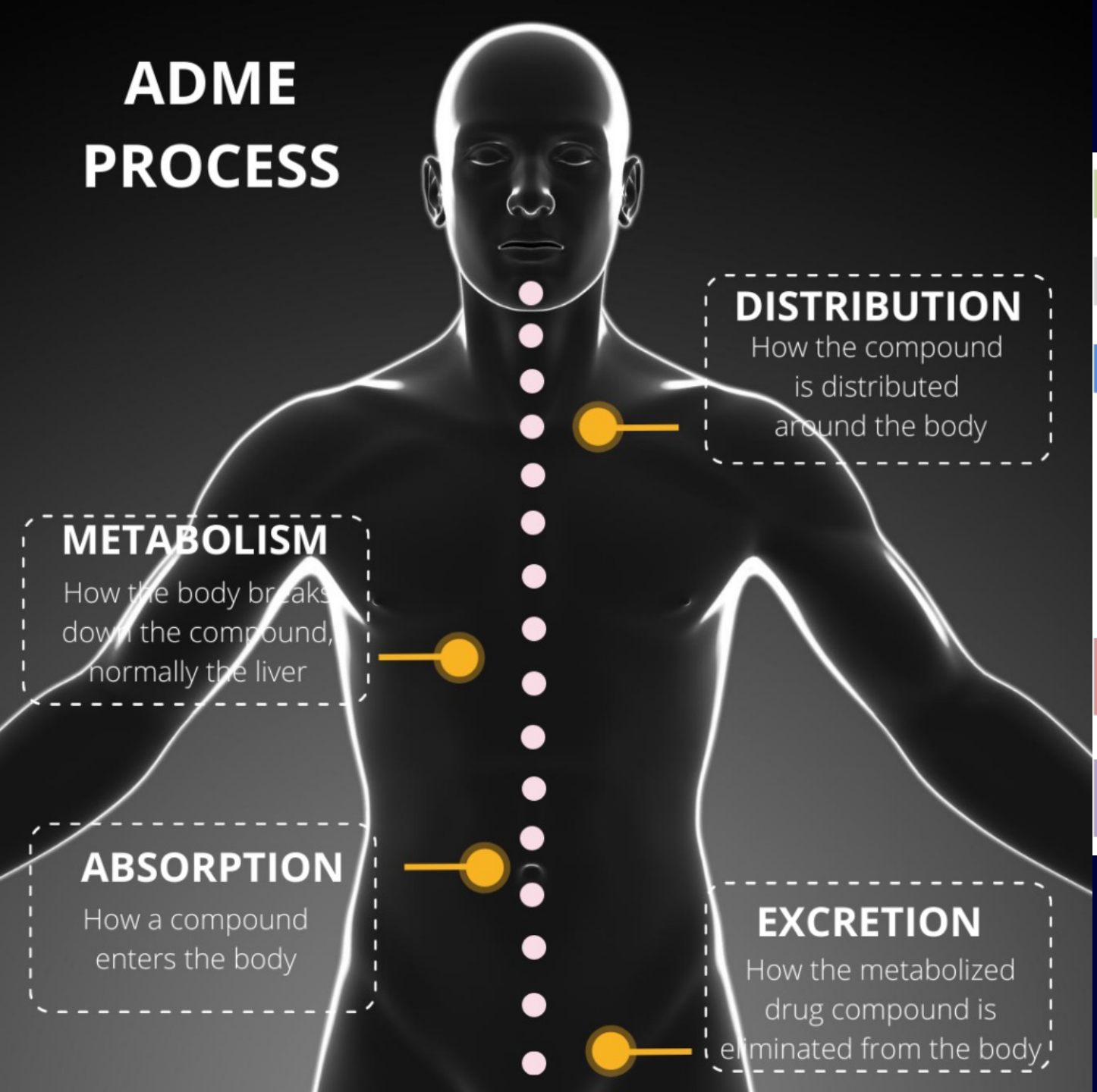
Exposure

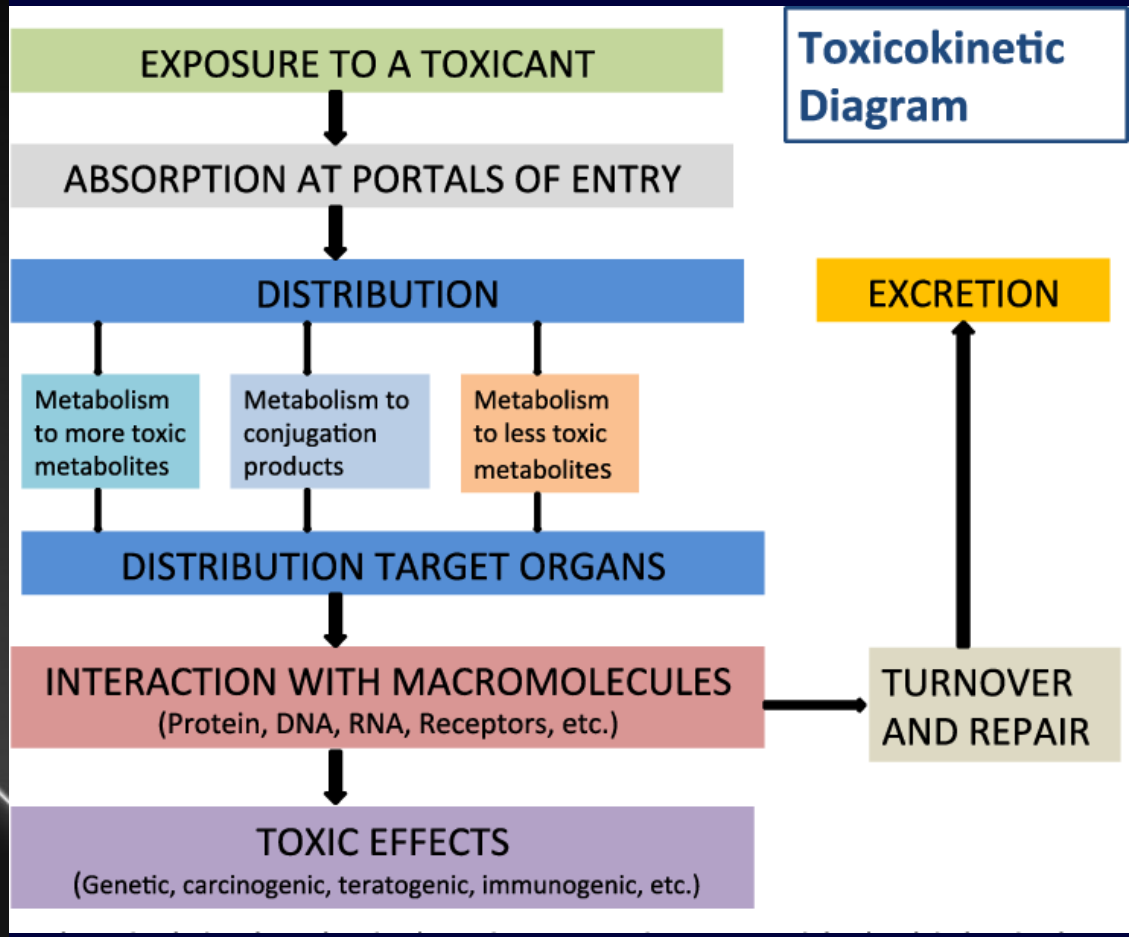
Genetics

- Antioxidants defences
- Xenobiotic metabolism
- Inflammation
- Repair / remodelling

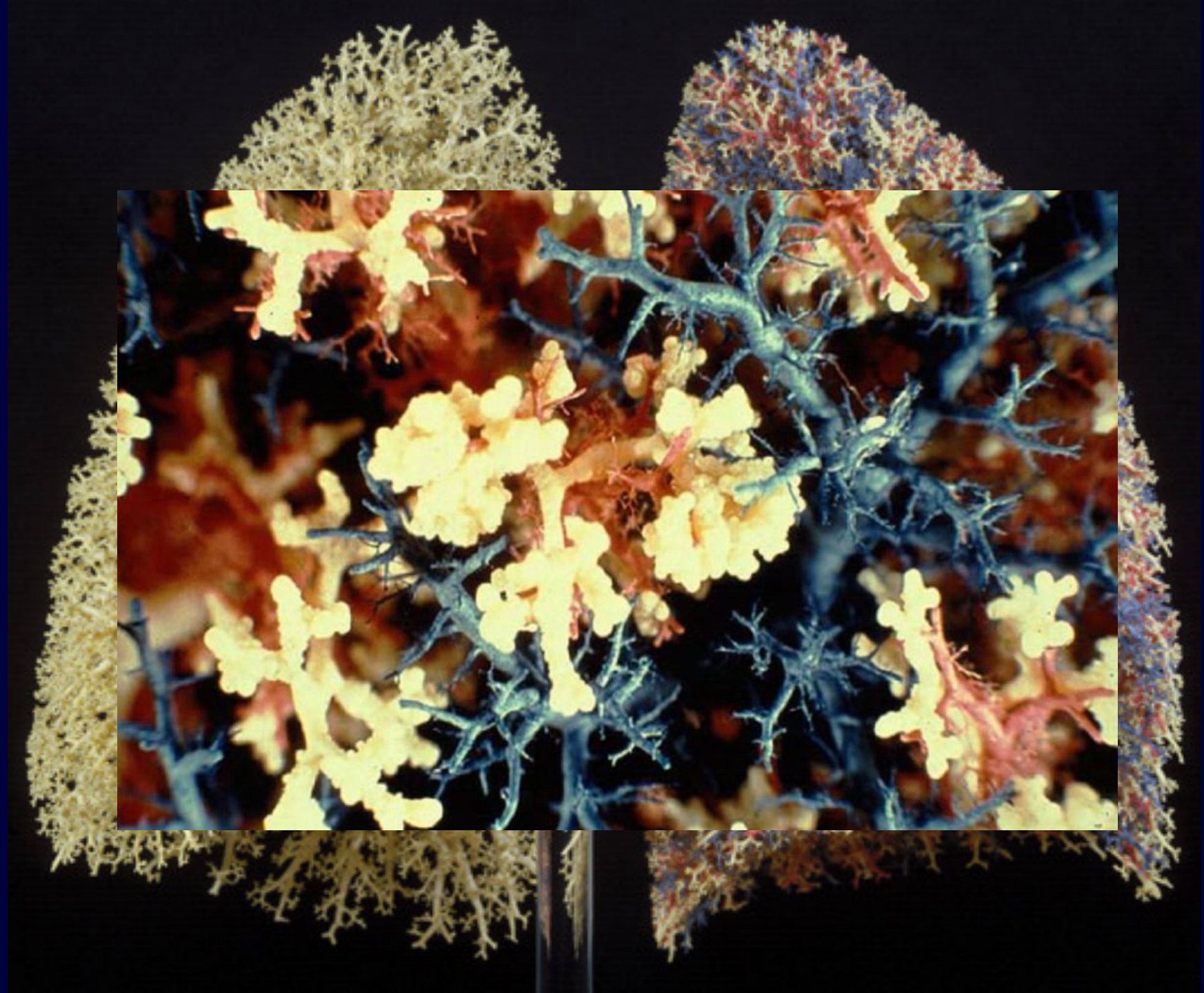
Probability of exposure



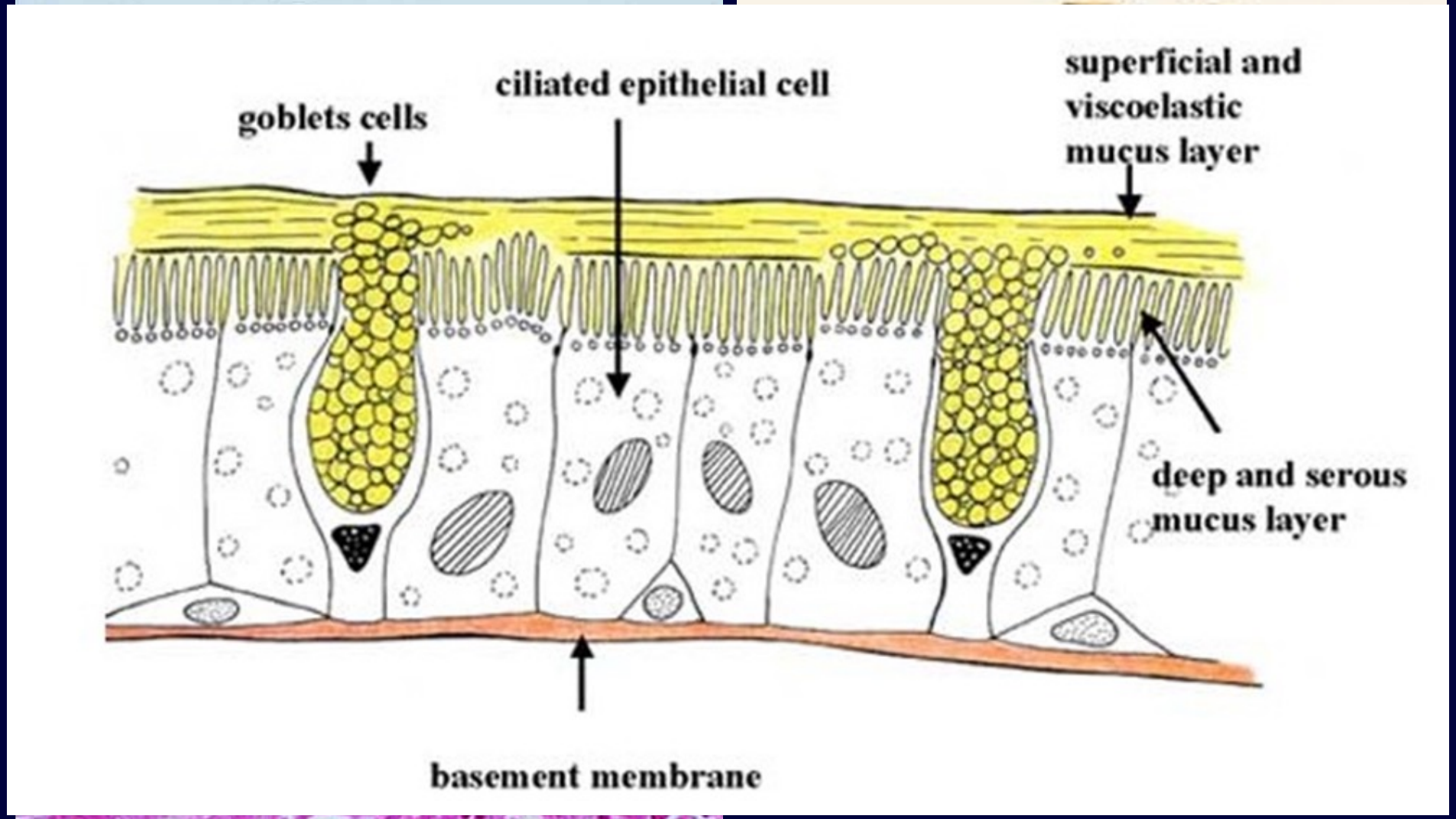


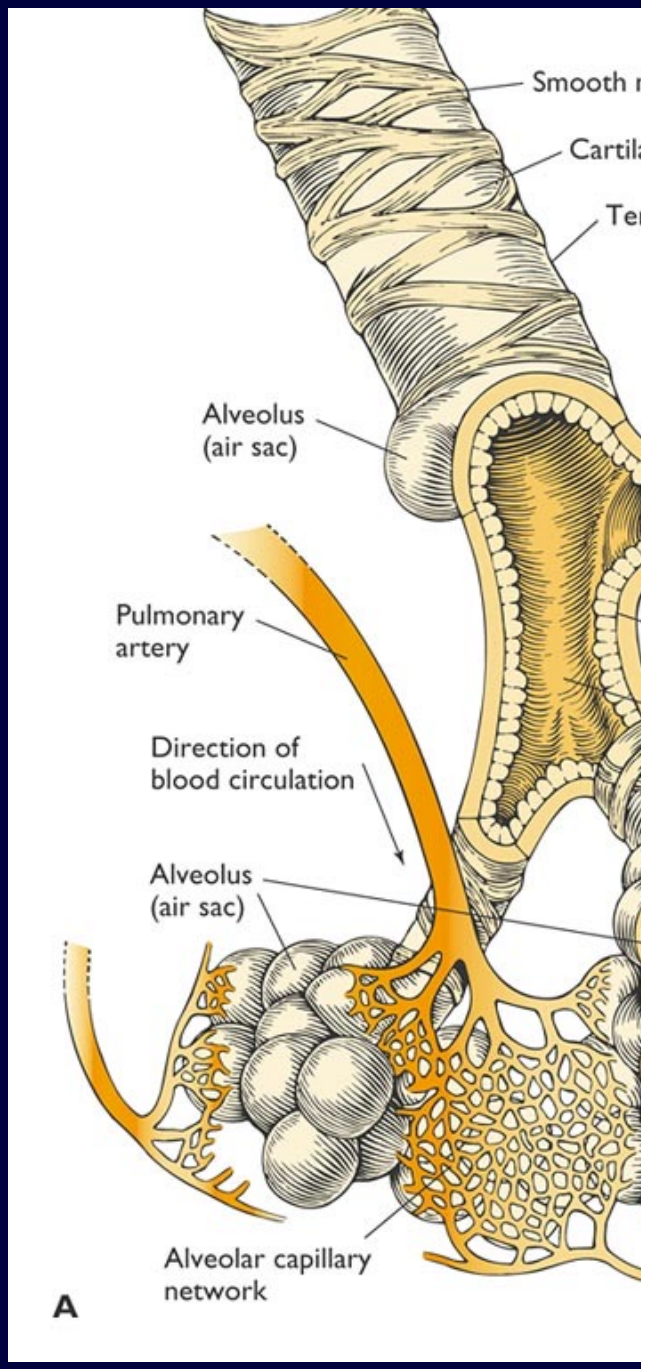


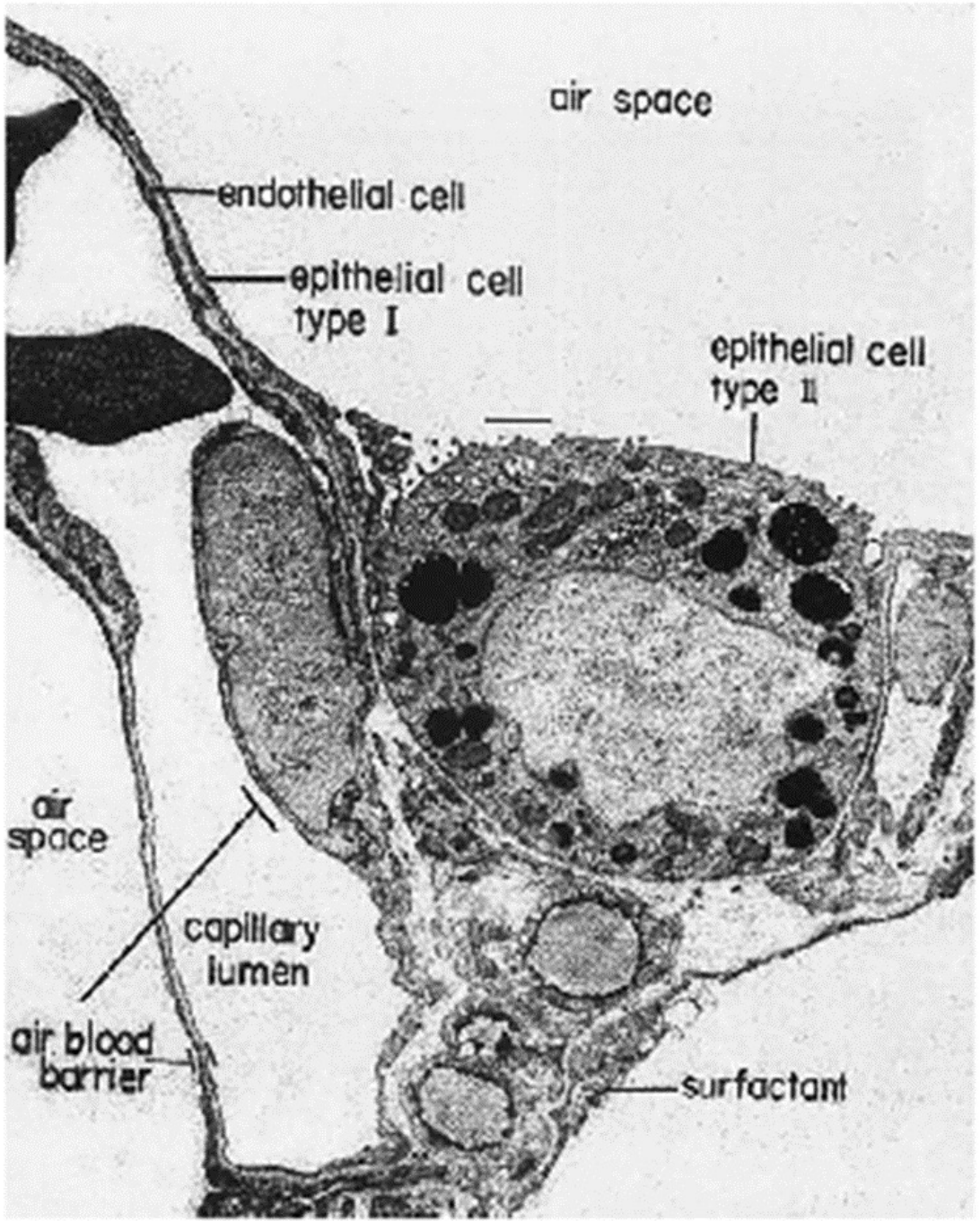
Alison J Falck et al. Pediatr Clin North Am. 2015; 62(5): 1173-97.

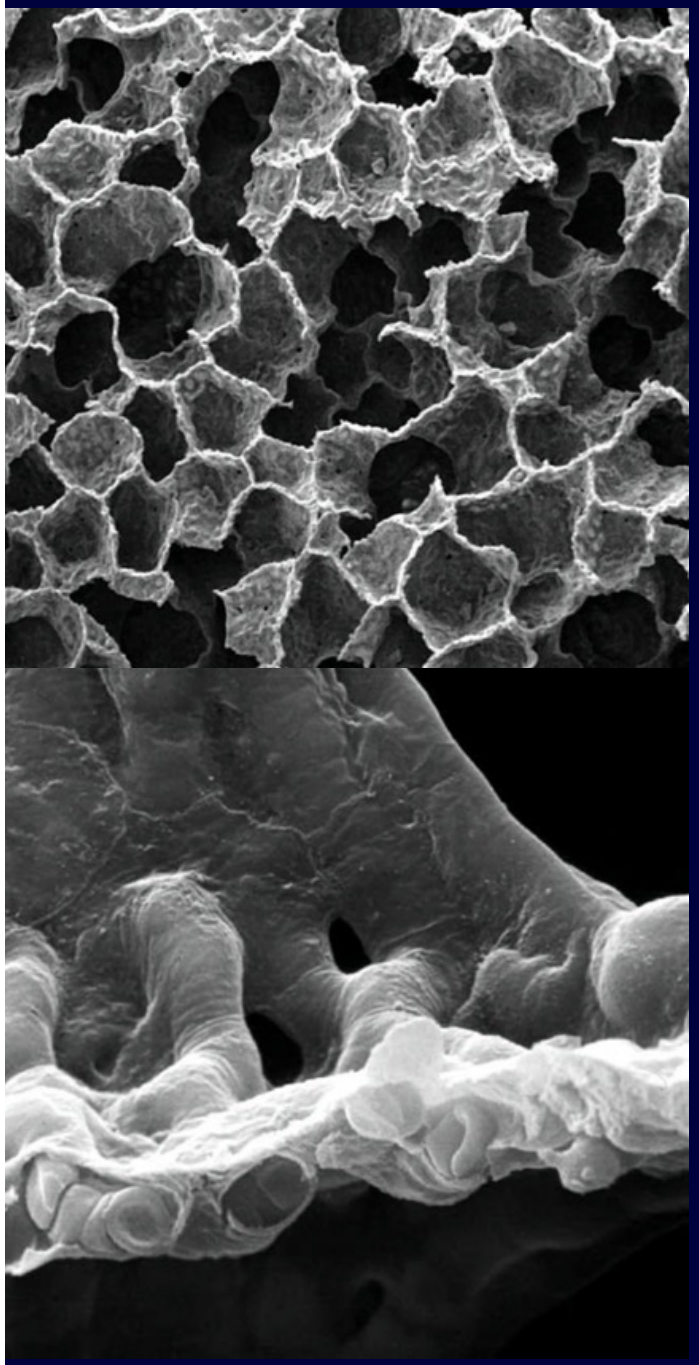


Conduction region - lung airways




Smooth
Cartil
Te
Alveolus
(air sac)
Pulmonary
artery
Direction of
blood circulation
Alveolus
(air sac)
Alveolar capillary
network
A

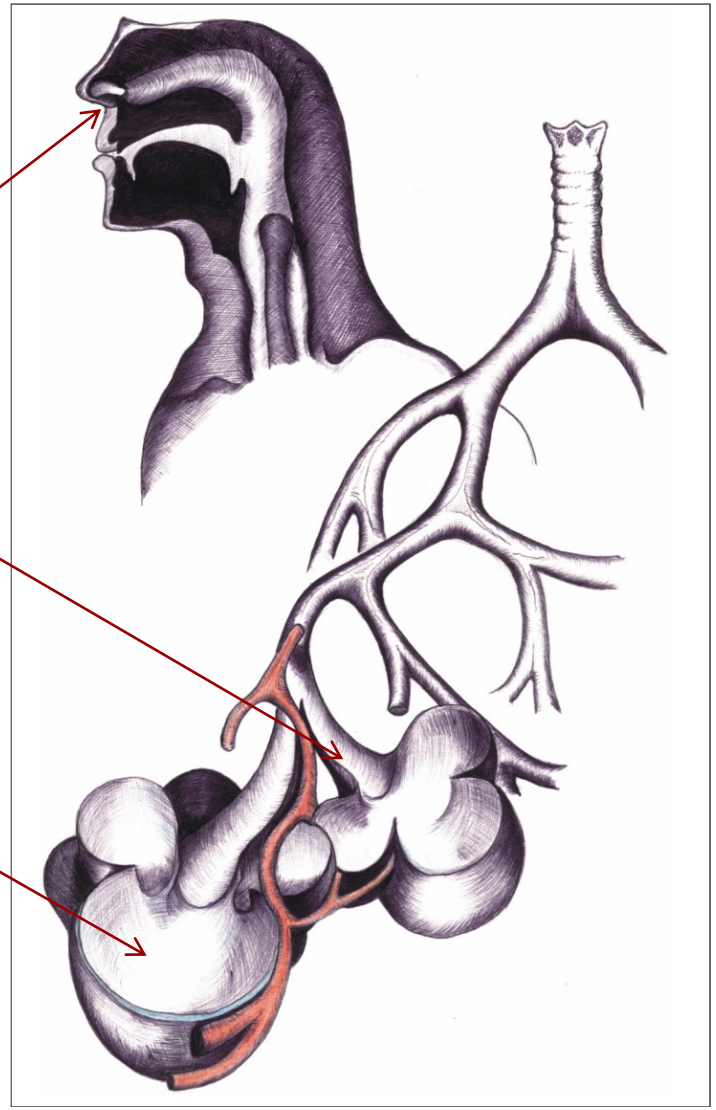

air space
endothelial cell
epithelial cell
type I
epithelial cell
type II
air
space
capillary
lumen
air blood
barrier
surfactant

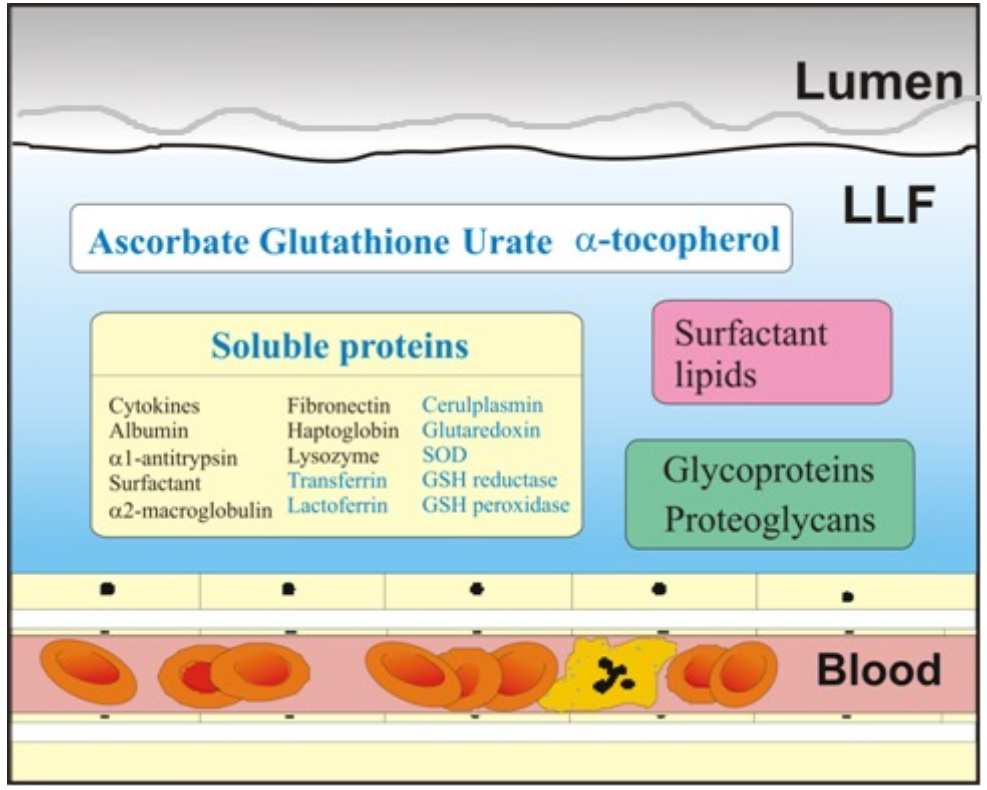


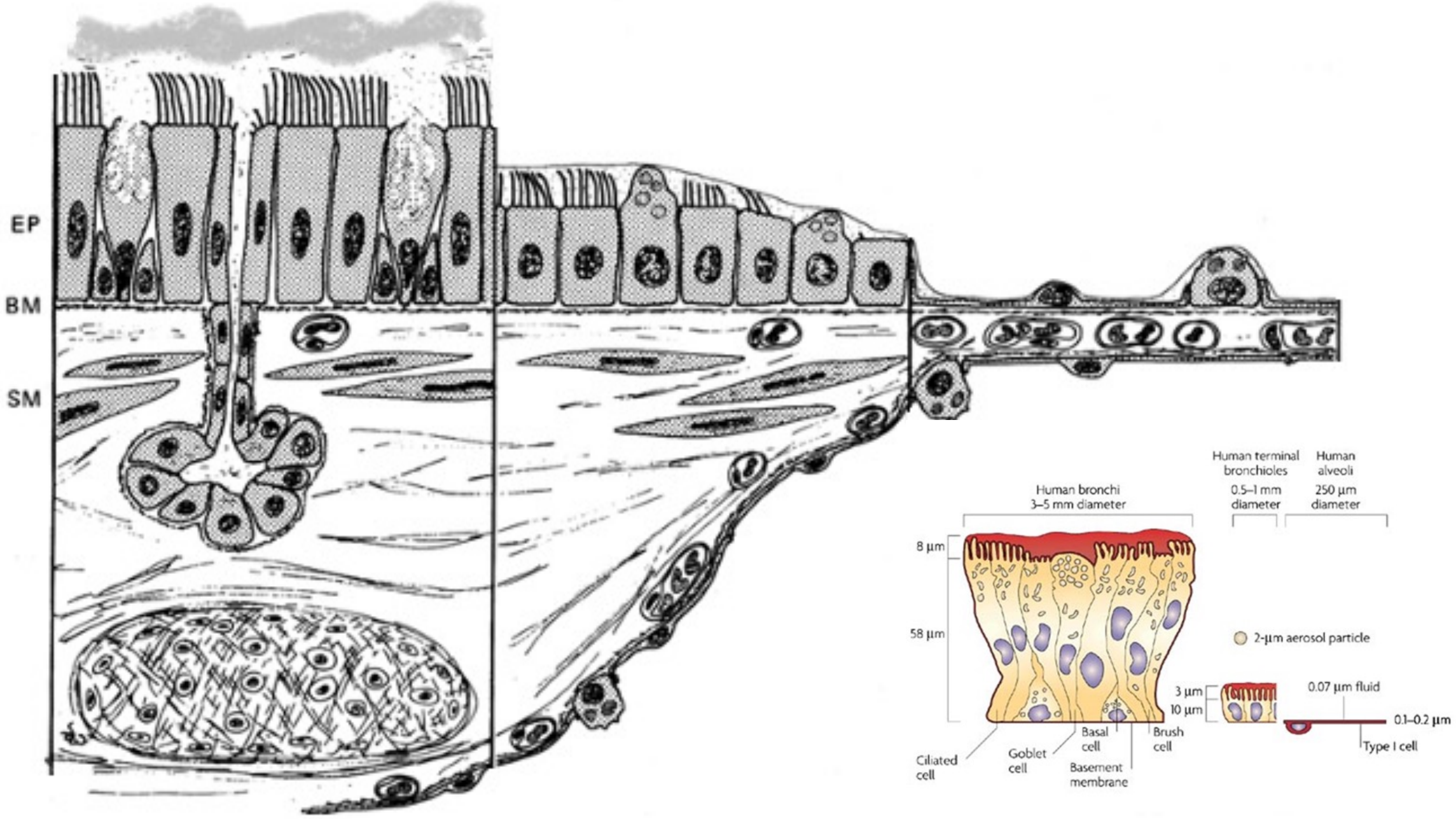
Nasal Lavage (NL)

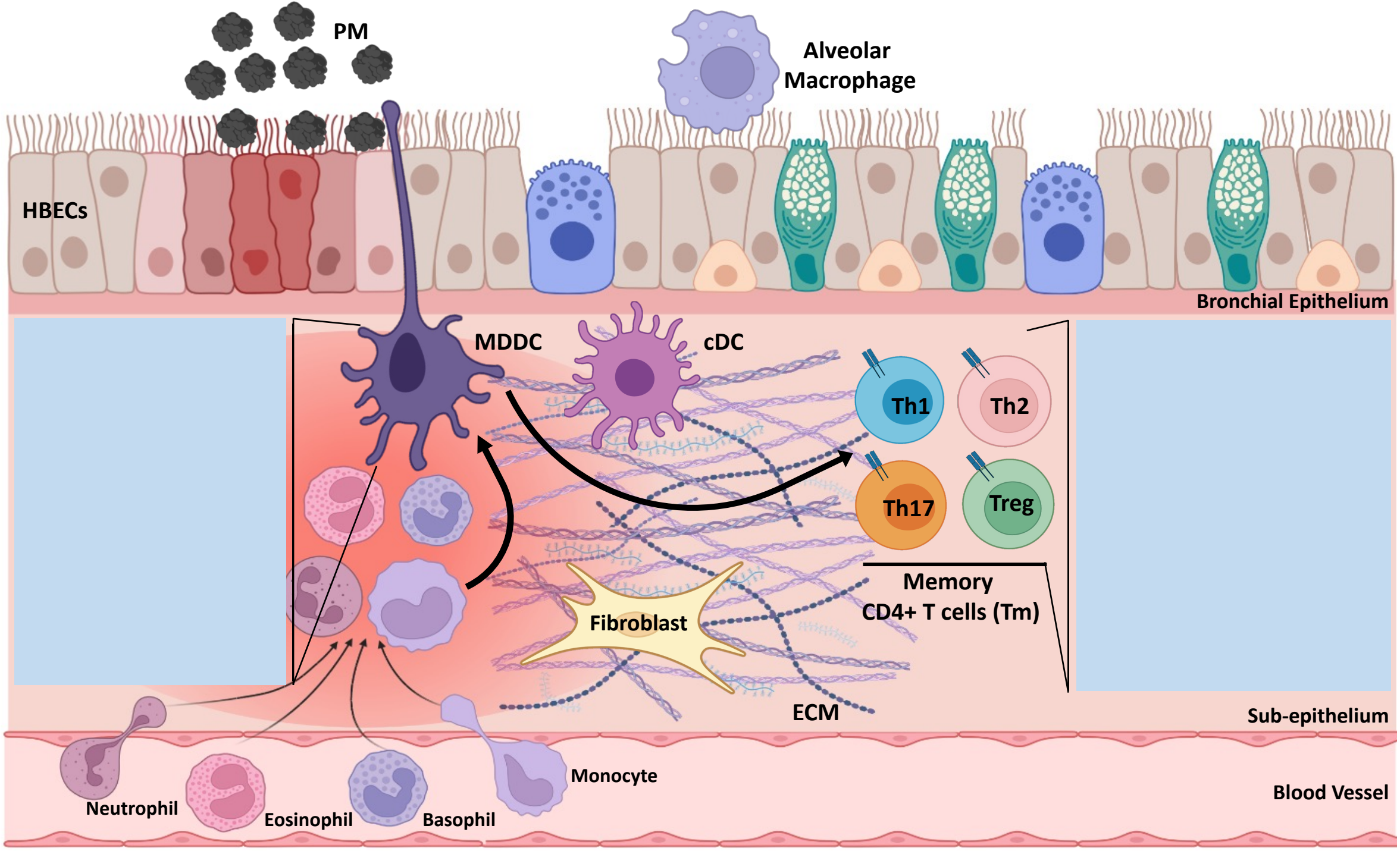
Bronchial Wash (BW)

Bronchoalveolar Lavage (BAL)

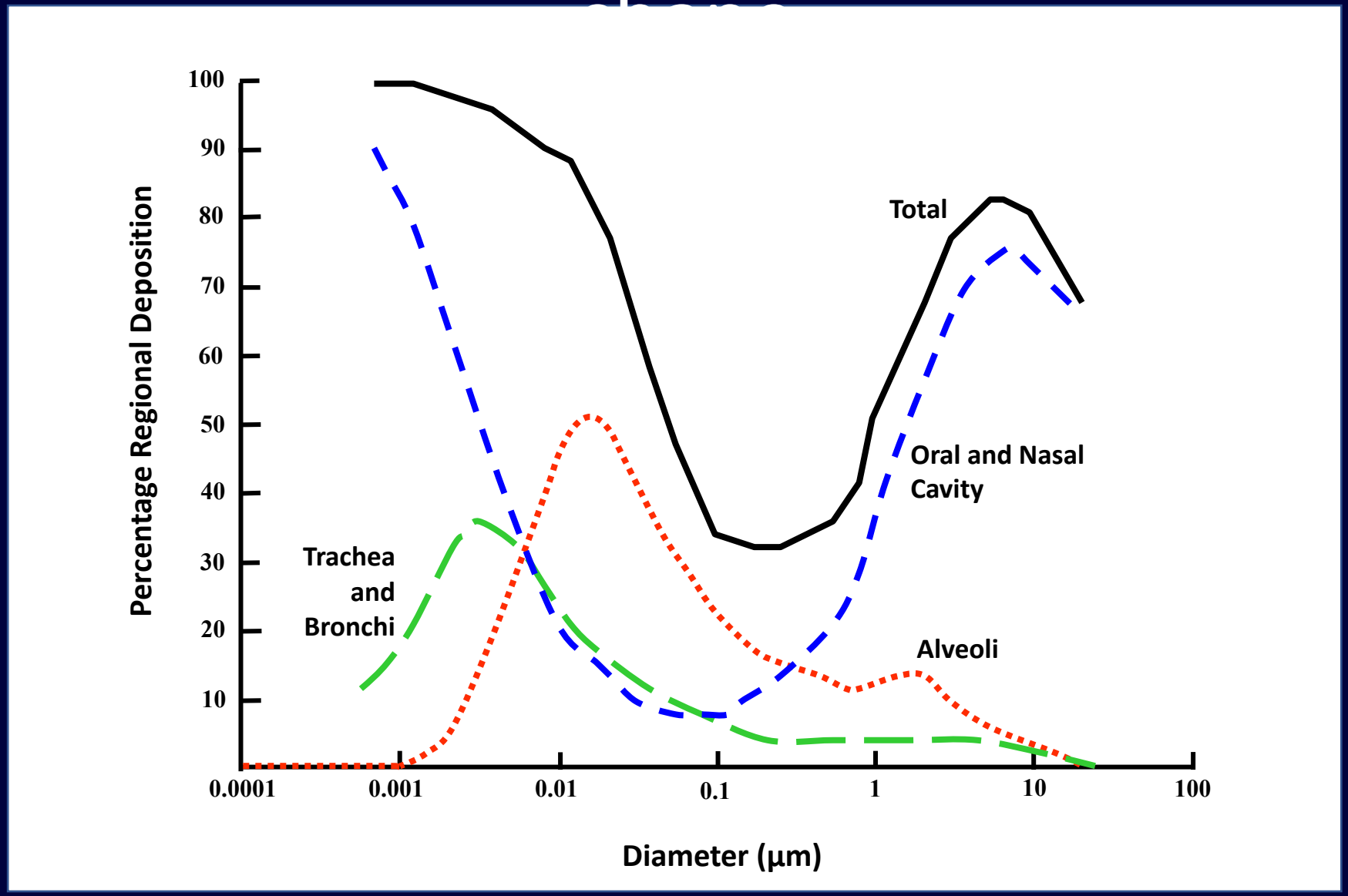




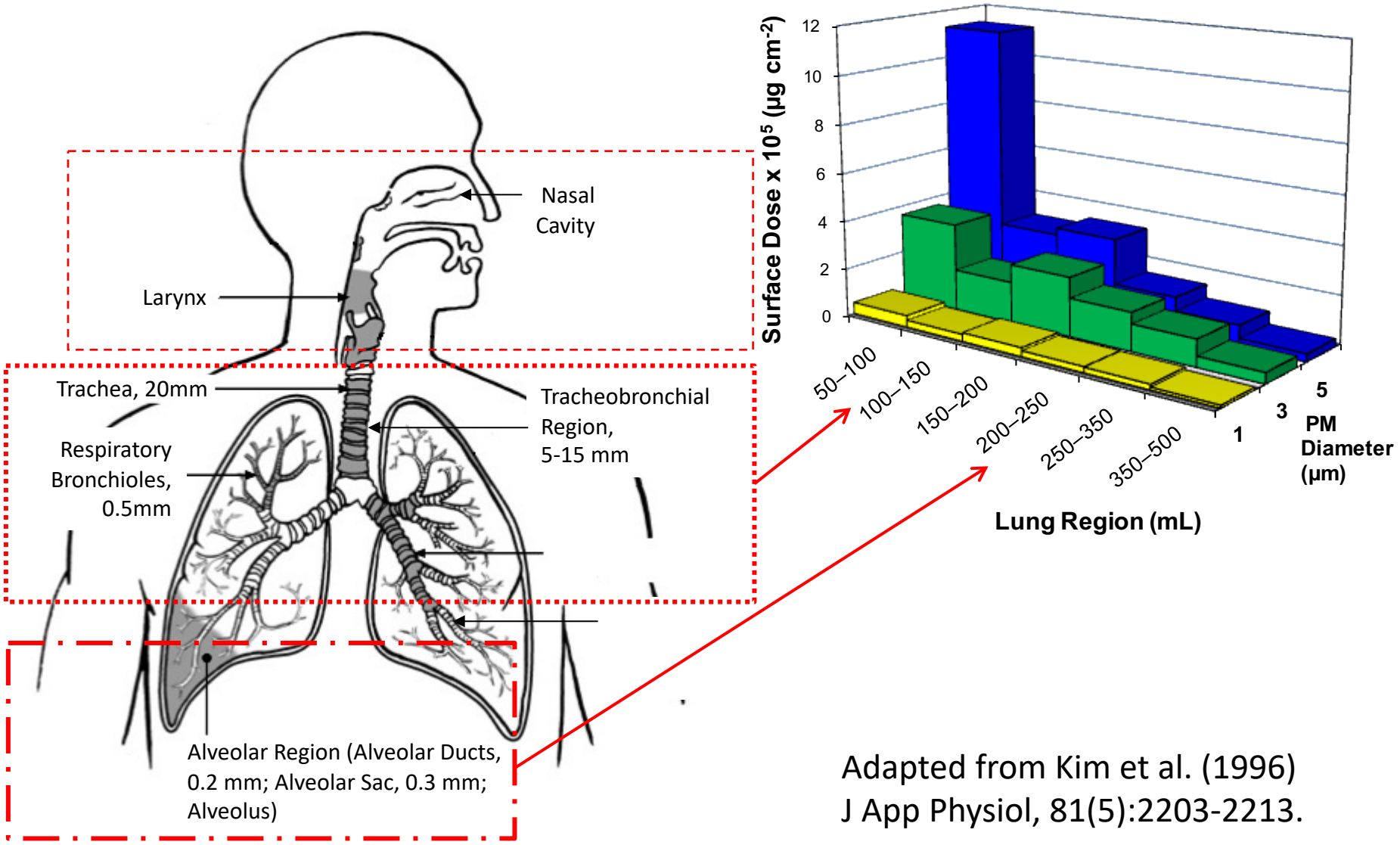

EP
BM
SM
Human bronchi
3–5 mm diameter
Human terminal
bronchioles
0.5–1 mm
diameter
Human
alveoli
250 µm
diameter
8 µm
58 µm
2-µm aerosol particle
3 µm
10 µm
0.07 µm fluid
0.1–0.2 µm
Type I cell
Ciliated
cell
Goblet
cell
Basal
cell
Basement
membrane
Brush
cell


PM
Alveolar Macrophage
HBECs
Bronchial Epithelium
MDDC
cDC
Th1
Th2
Th17
Treg
Memory
CD4+ T cells (Tm)
Fibroblast
ECM
Sub-epithelium
Monocyte
Neutrophil
Eosinophil
Basophil
Blood Vessel

Deposition depends on size and shape



Dose depends on the site of deposition



Adapted from Kim et al. (1996)
J App Physiol, 81(5):2203-2213.

Problems of lung functional anatomy

1. Epithelial cells lining airways and alveoli are not highly exfoliative & require specific cellular regeneration & repair after serious damage

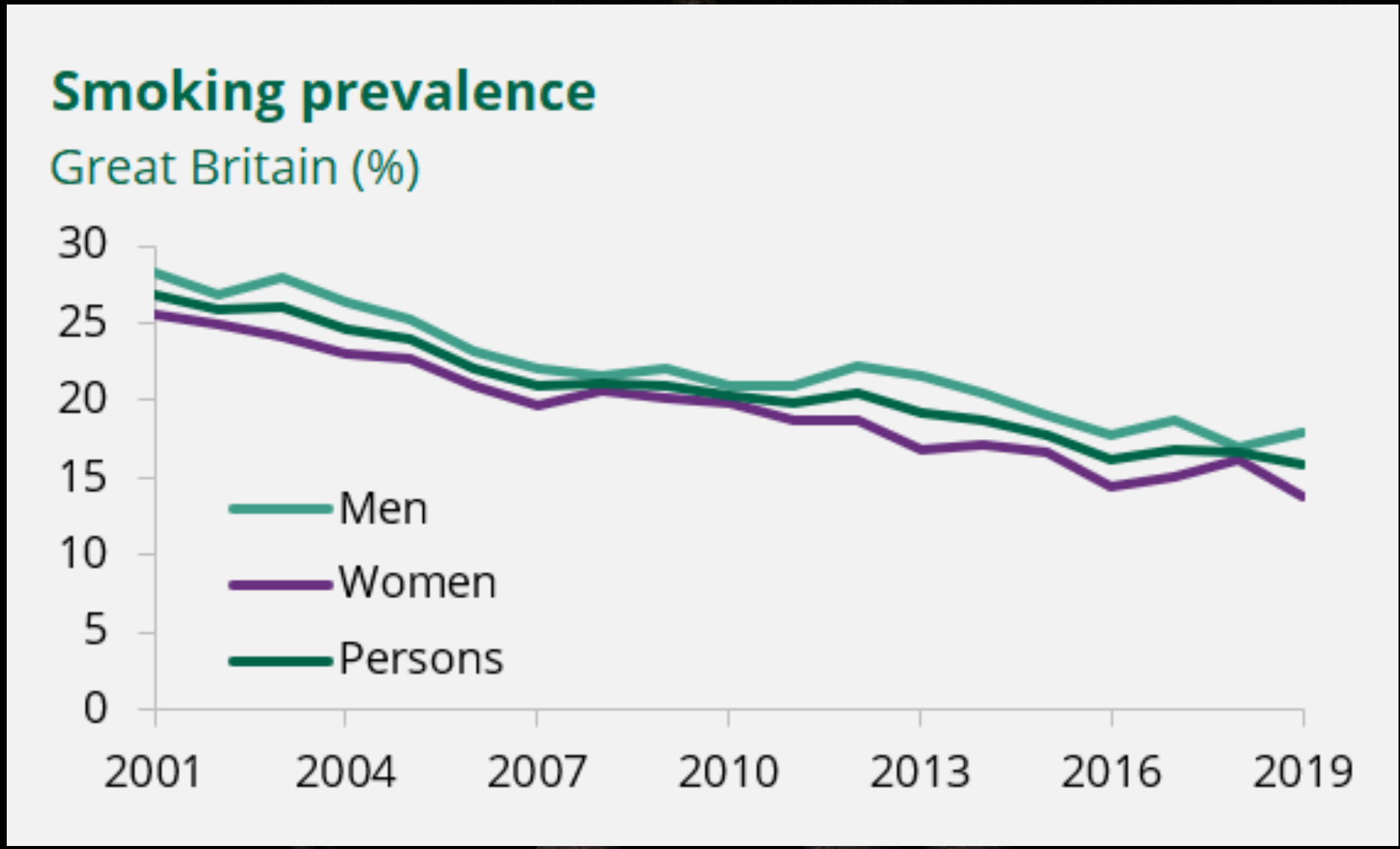
2. The large tidal volume of external air (roughly 8 cu meters per day) tidal air flow -- not a flow-through system -- airborne particles can accumulate

3. The branching and narrowing of airways traps particulate matter

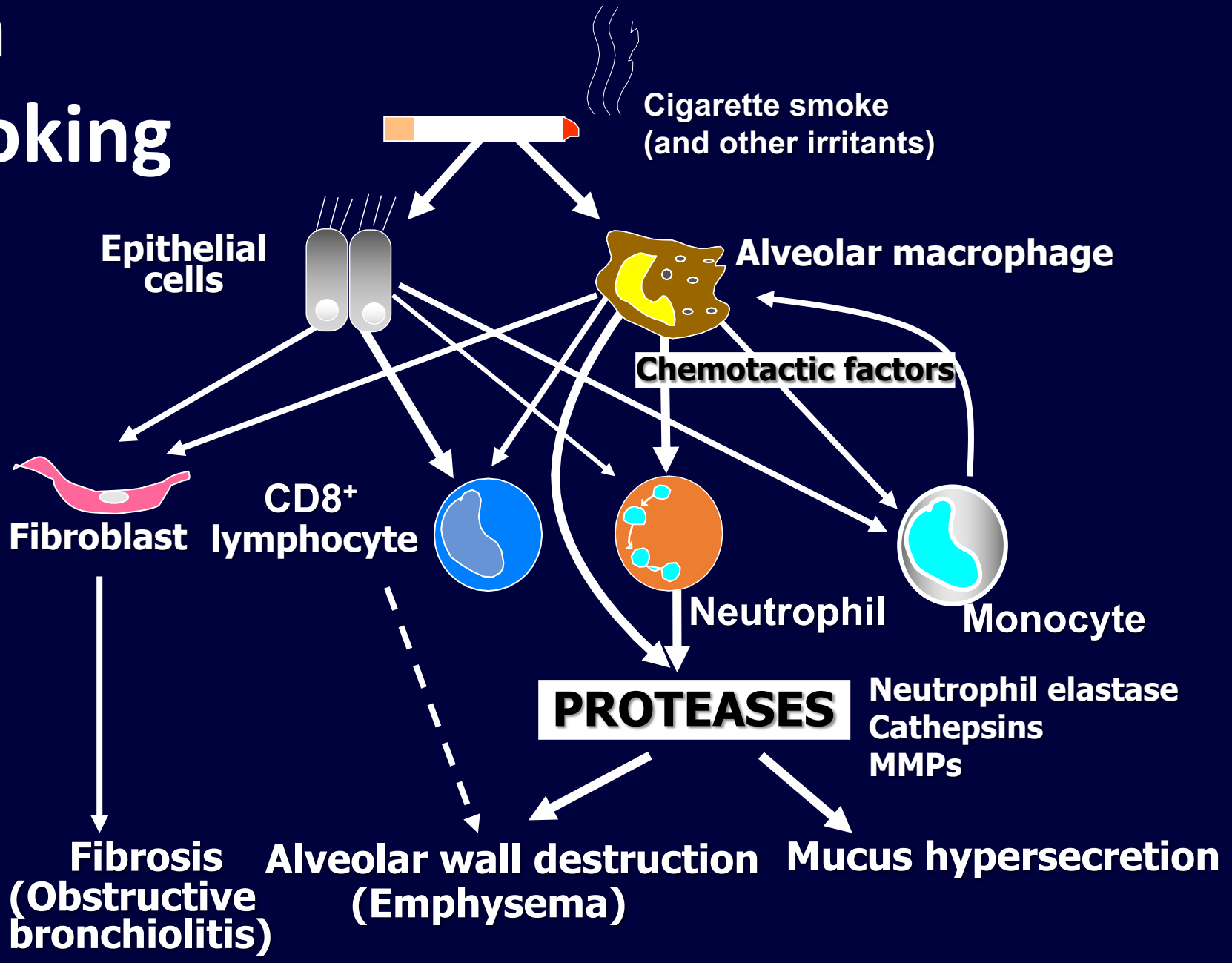
4. Lung immune cells (macrophages, neutrophils) can produce lung injury via inflammatory mediators and reactive oxygen species (ROS)

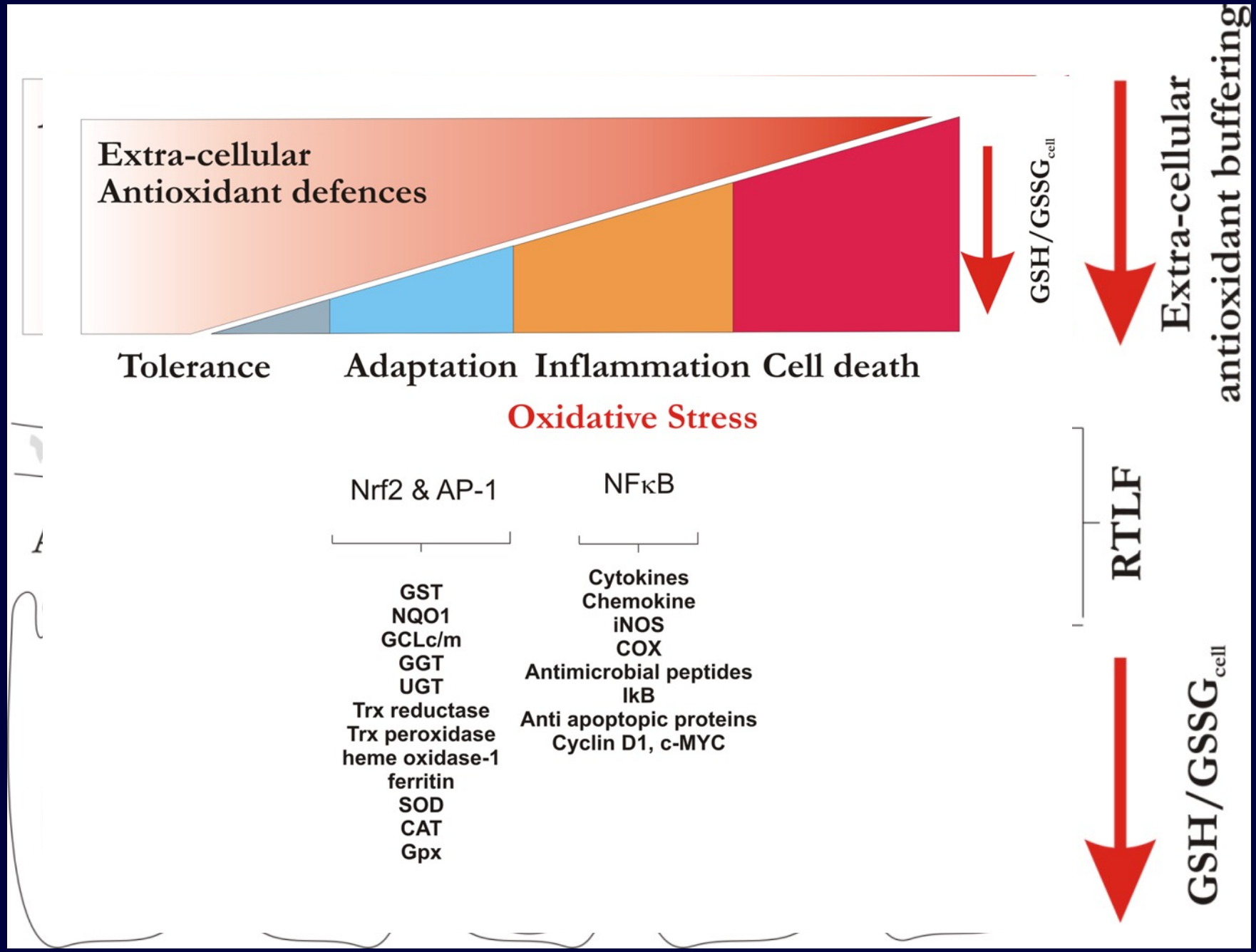
5. High pO2

6. Lungs often exposed to high conc of *reactive oxygen species* (ROS)
   external - oxidant gases such as ozone, nitrogen dioxide, particulate matter
   internal - produced by lung cells/tissues in response to irritants or noxious agents

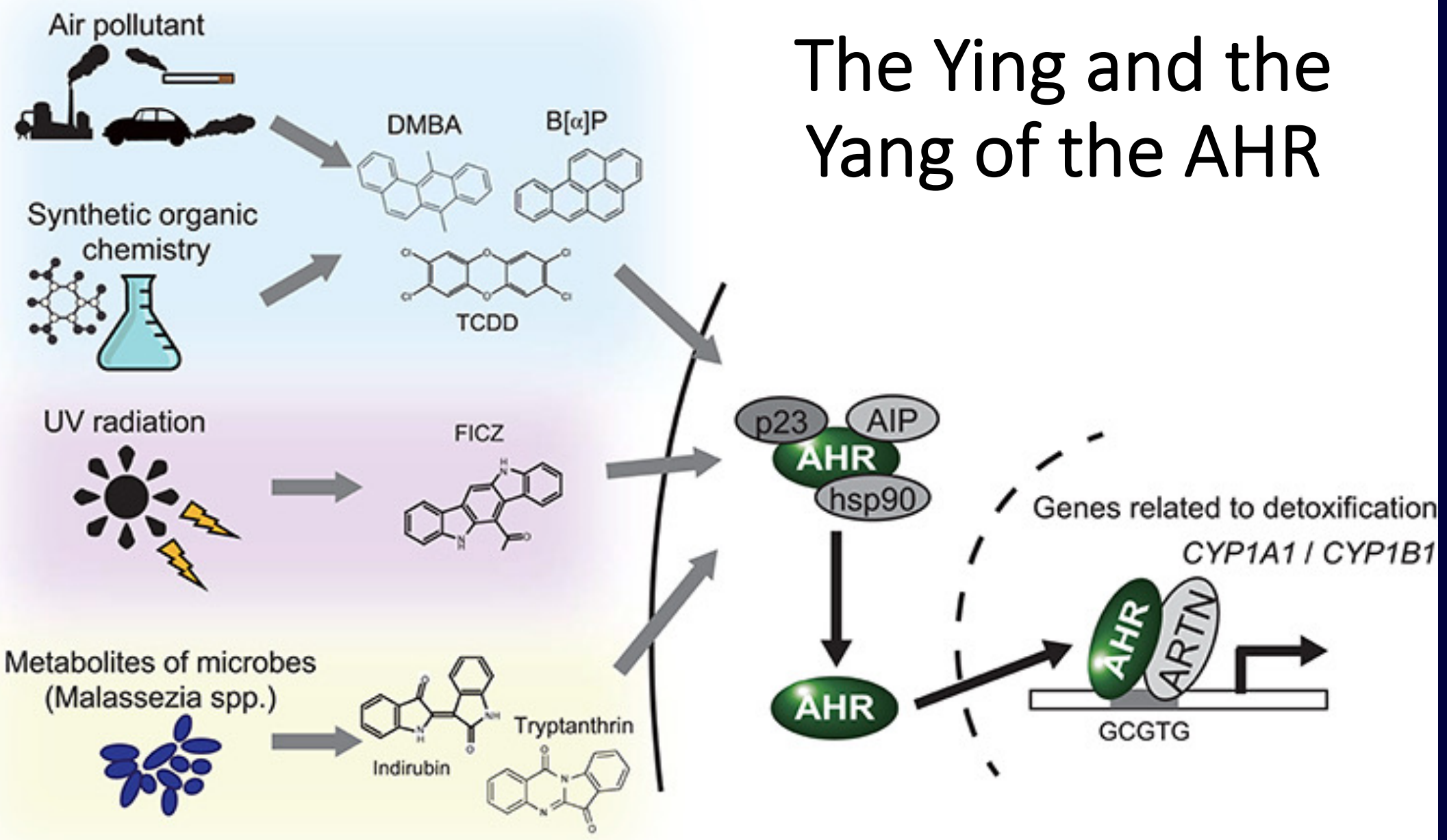

Smoking prevalence
Great Britain (%)
30
25
20
15
10
5
0
Men
Women
Persons
2001
2004
2007
2010
2013
2016
2019

Lessons from cigarette smoking



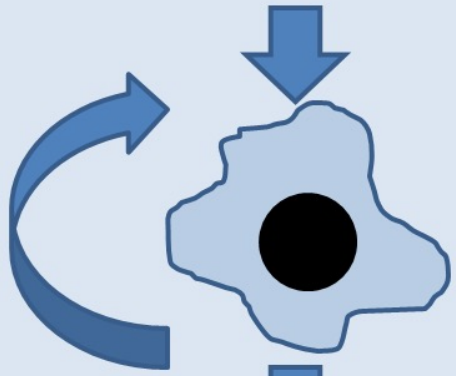

Extra-cellular
Antioxidant defences
GSH/GSSG$_{cell}$
Extra-cellular
antioxidant buffering
Tolerance
Adaptation
Inflammation
Cell death
Oxidative Stress
Nrf2 & AP-1
NFκB
GST
NQO1
GCLc/m
GGT
UGT
Trx reductase
Trx peroxidase
heme oxidase-1
ferritin
SOD
CAT
Gpx
Cytokines
Chemokine
iNOS
COX
Antimicrobial peptides
IkB
Anti apoptopic proteins
Cyclin D1, c-MYC
RTLF
GSH/GSSG$_{cell}$

The Ying and the Yang of the AHR



Physical Chemical Infectious Immunologic

Stress



Adaption

Biochemical

Cellular growth

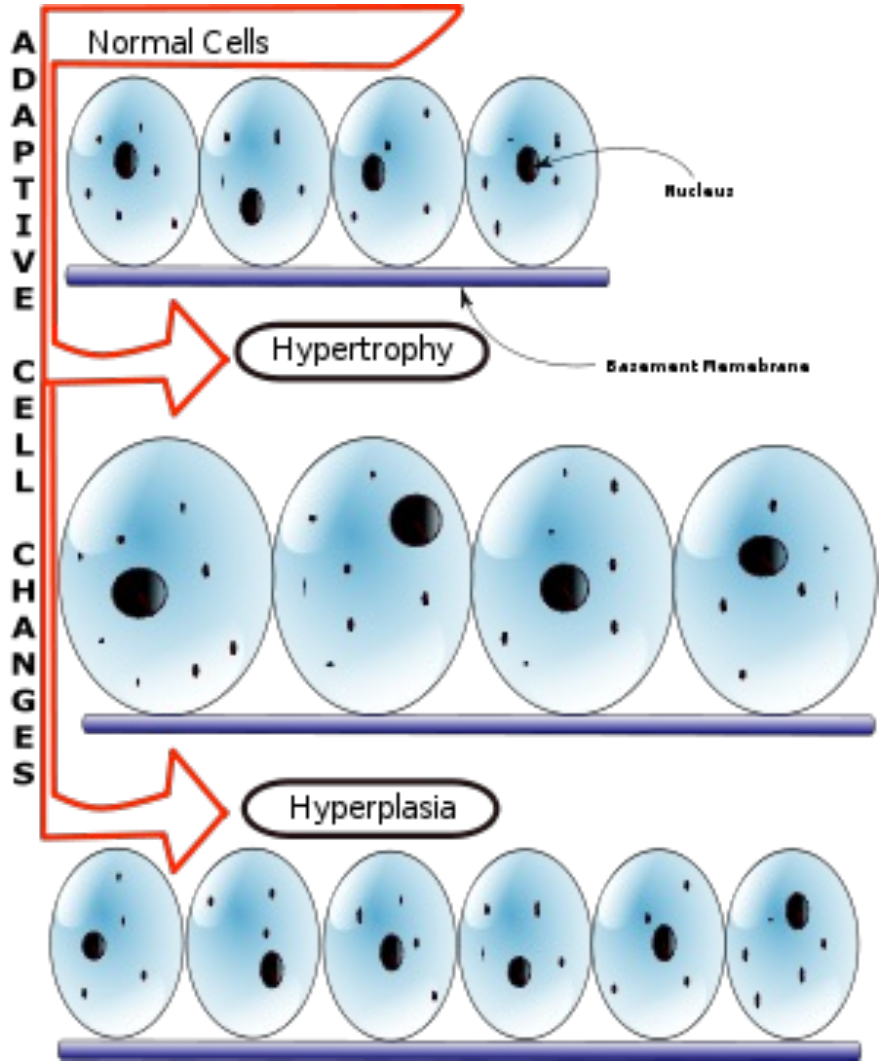
Injury

Cell death

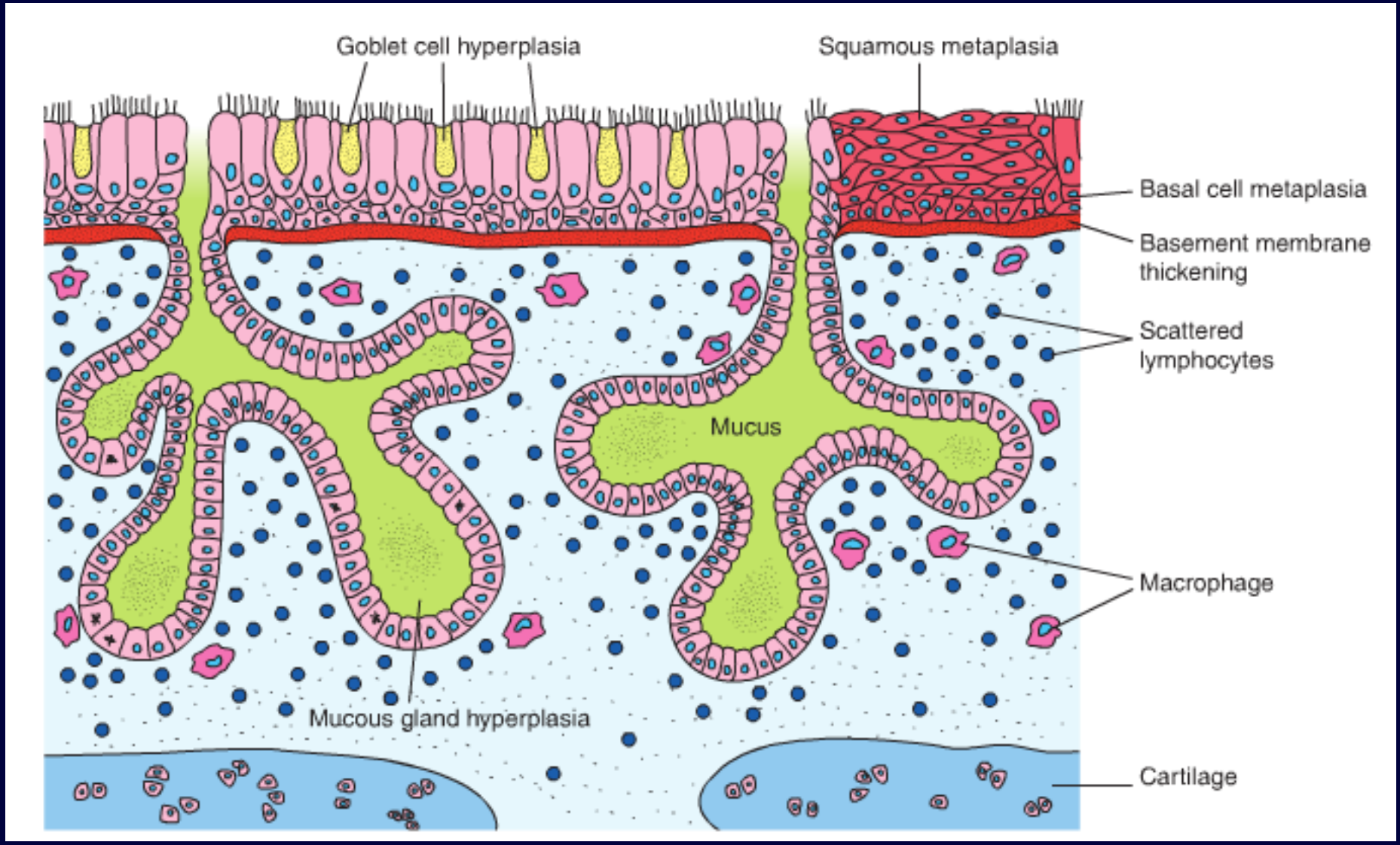
Necrosis Apoptosis

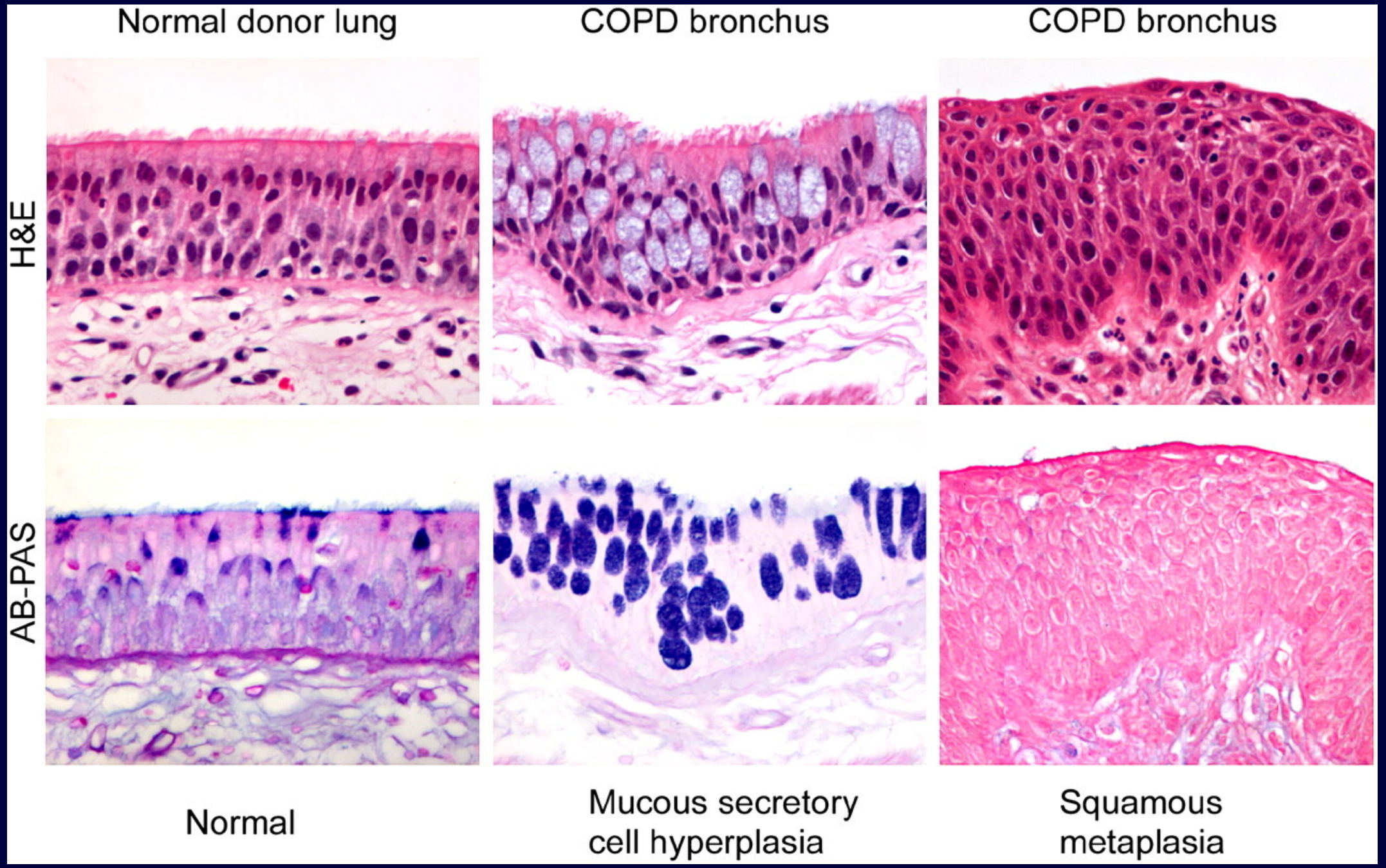
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia
Intracellular storage

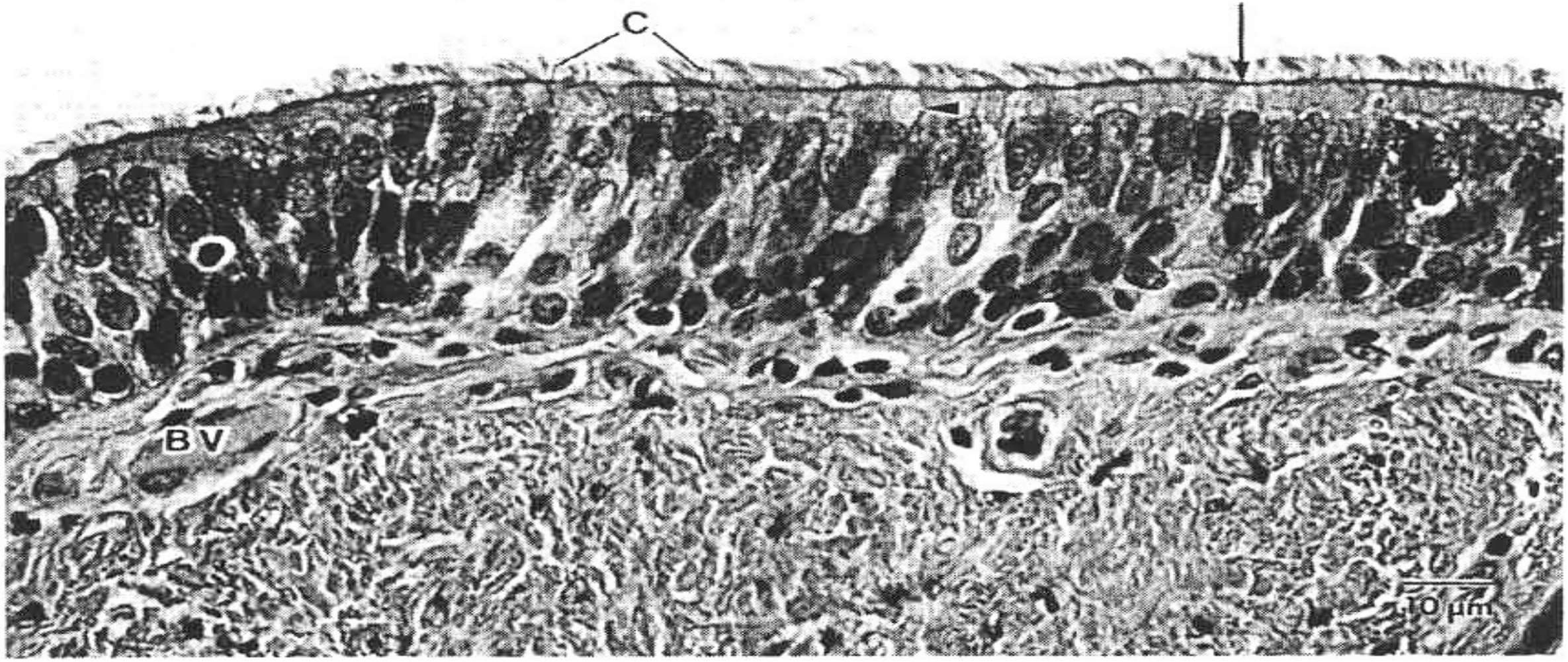
Neoplasia



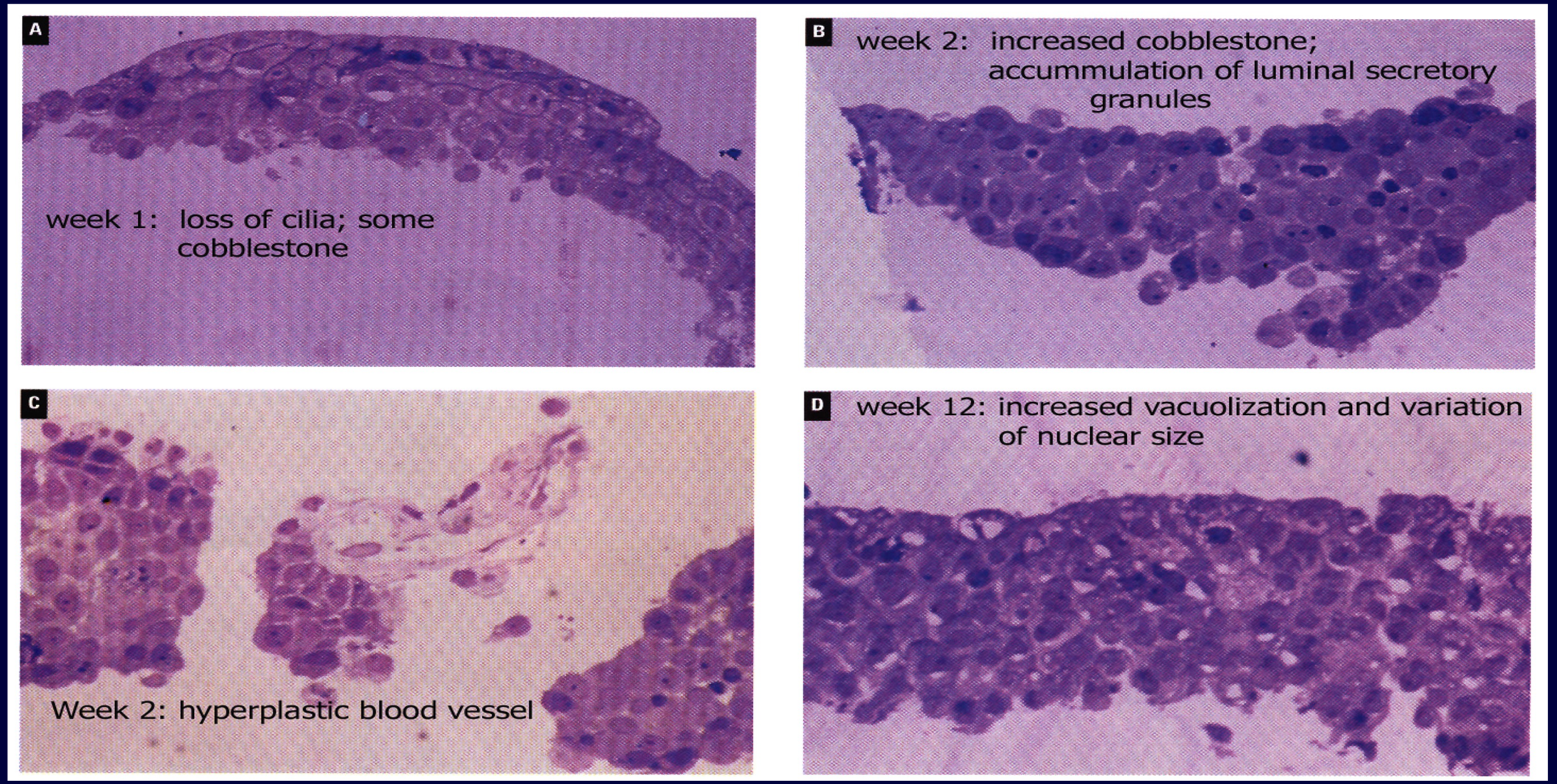
Morphologic changes in chronic bronchitis



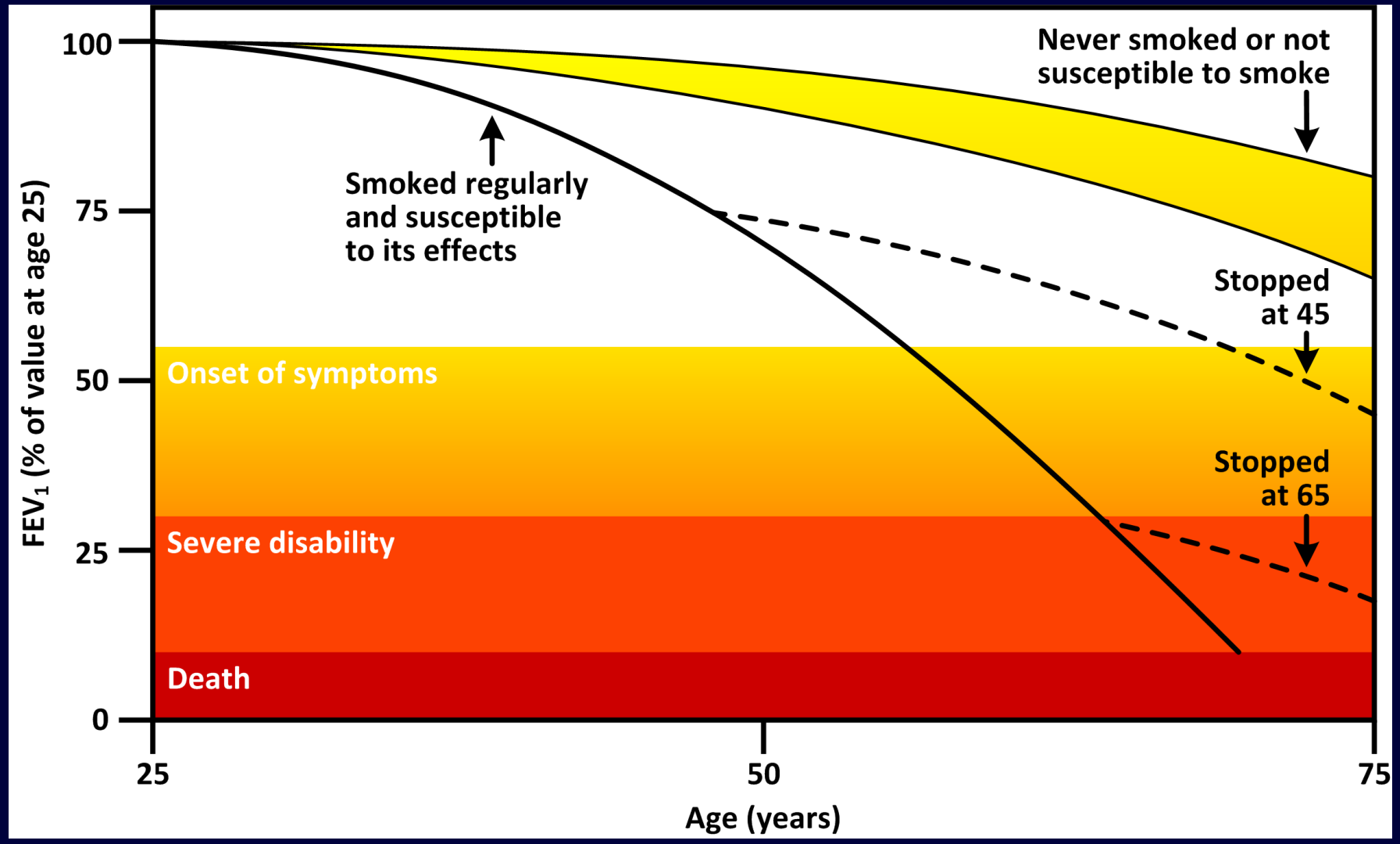

Normal donor lung
COPD bronchus
COPD bronchus
H&E
AB-PAS
Normal
Mucous secretory cell hyperplasia
Squamous metaplasia


C
BV
10 µm

Effects of Ozone on Nasal Mucosa 22-Year-Old Male Migrant to Mexico City

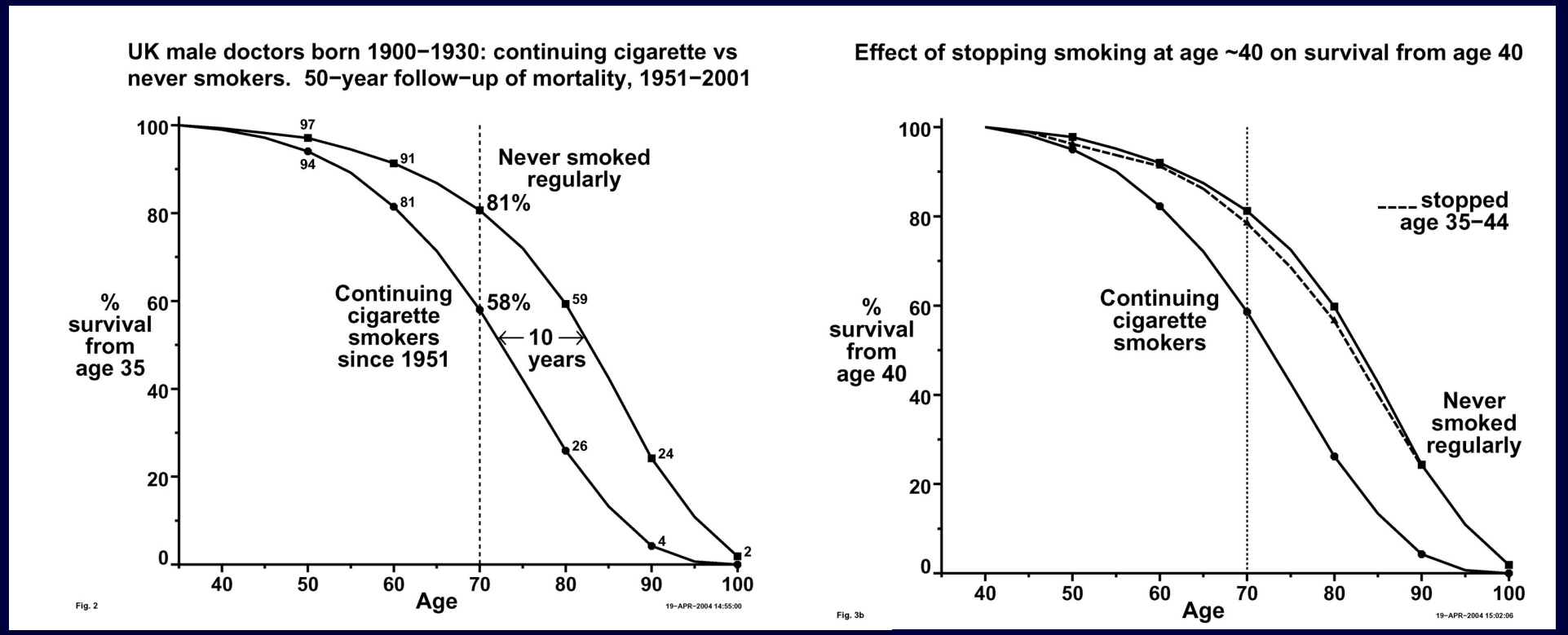


The Fletcher Curve



Hazard of cigarette smoking (in men)

- Many young men started smoking in the first few decades of the 20th century, so full lifelong risks among men are now known.
- Young women started smoking substantial numbers of cigarettes just after the mid-20th century, so full hazards in later middle age among women have become apparent only in the 21st century

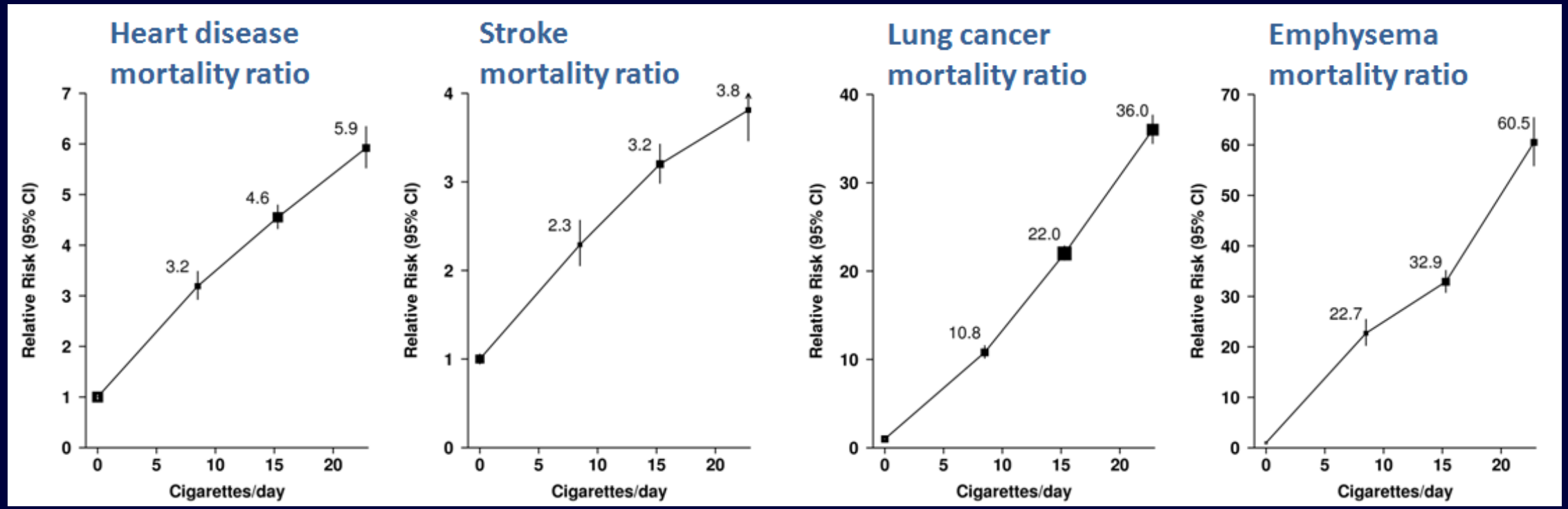


BMJ 2004; **328:** 1519

Hazard of cigarette smoking (in women)

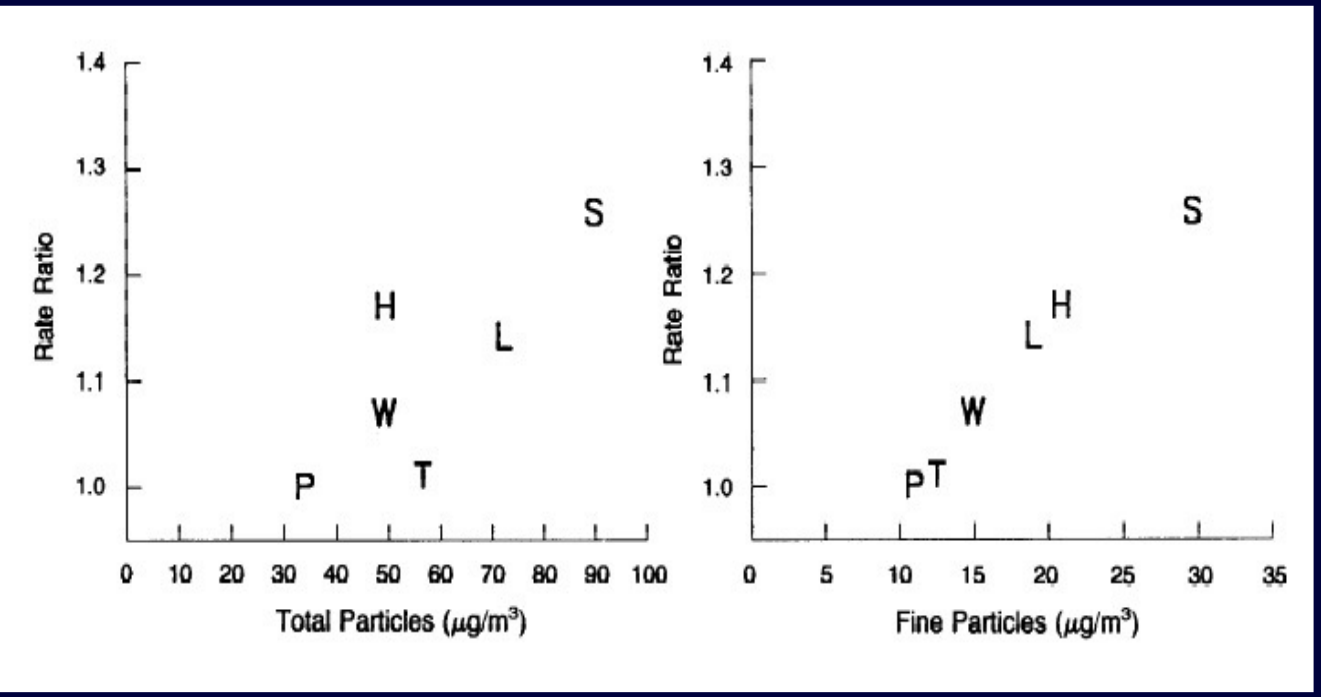
THE UK MILLION WOMEN STUDY. Valerie Beral, Kirstin Pirie, Richard Peto. Lancet 2013; 381: 133-41

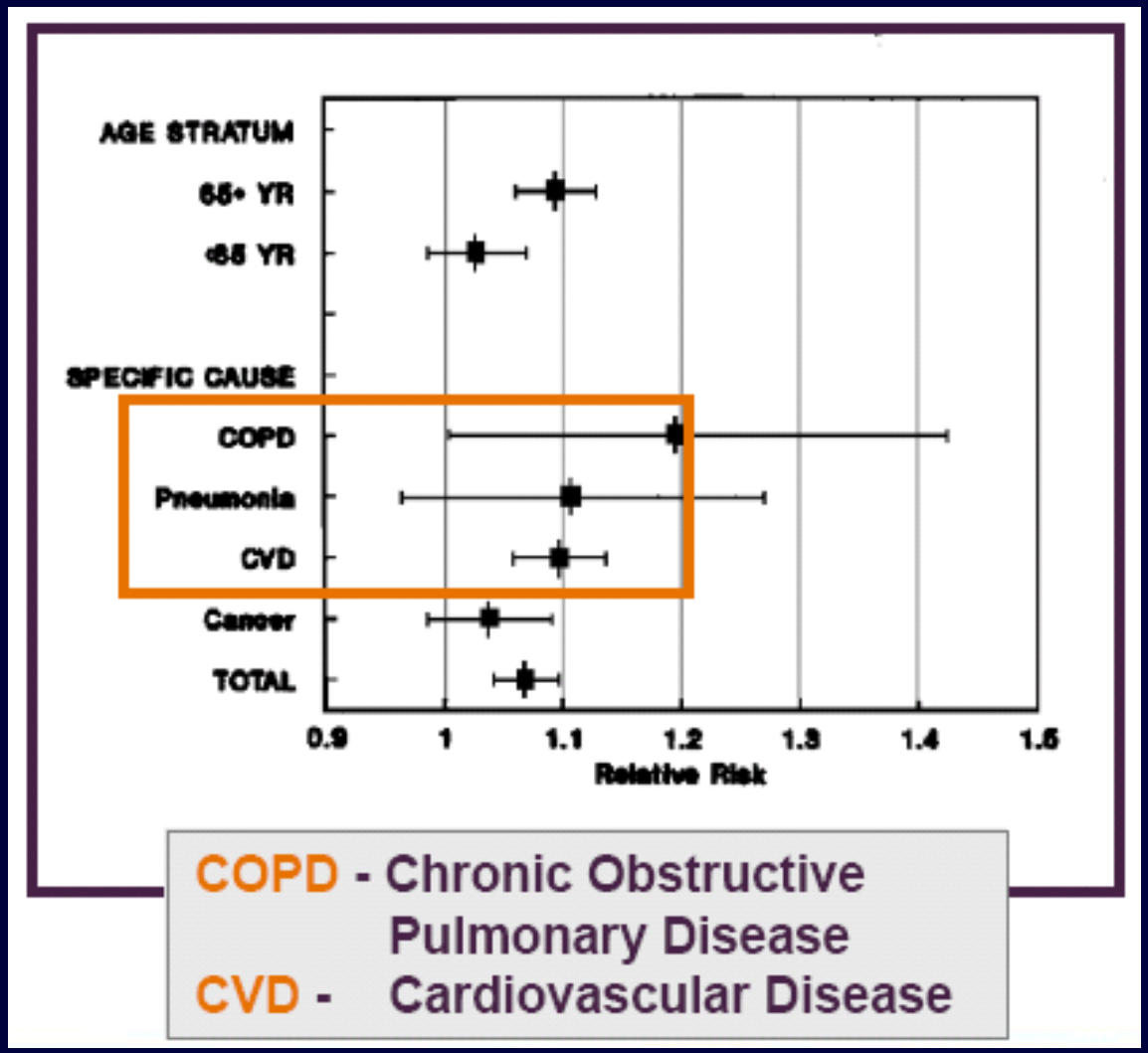
First large prospective study of women who have smoked throughout adult life



Cigarette smoke risks vs. $PM_{2.5}$

Data from the 6-cities study





Cigarette smoke risks vs. $PM_{2.5}$

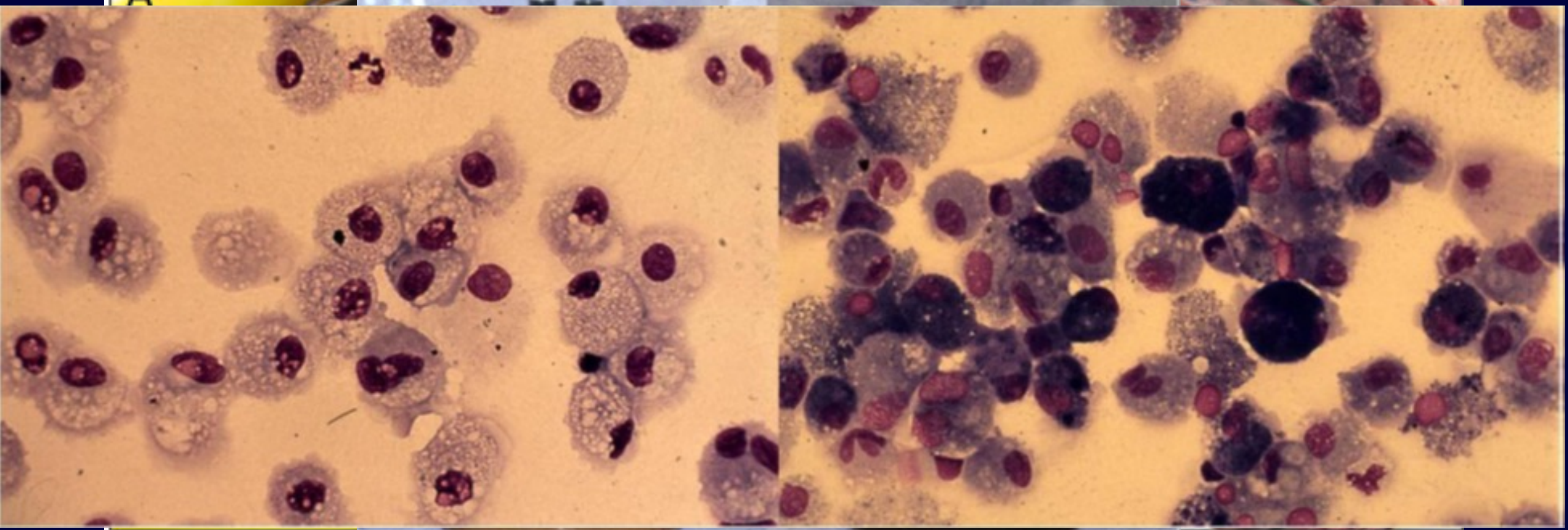
Table 5. Adjusted Mortality-Rate Ratios for Current and Former Cigarette Smokers and for the Most Polluted City as Compared with the Least Polluted, According to Cause of Death.*

Cause of Death	Percentage of Total	Current Smokers†	Former Smokers‡	Most vs. Least Polluted City
			rate ratio (95% CI)	
All	100	2.00 (1.51–2.65)	1.39 (1.10–1.75)	1.26 (1.08–1.47)
Lung cancer	8.4	8.00 (2.97–21.6)	2.54 (0.90–7.18)	1.37 (0.81–2.31)
Cardiopulmonary disease	53.1	2.30 (1.56–3.41)	1.52 (1.10–2.10)	1.37 (1.11–1.68)
All others	38.5	1.46 (0.89–2.39)	1.17 (0.80–1.73)	1.01 (0.79–1.30)

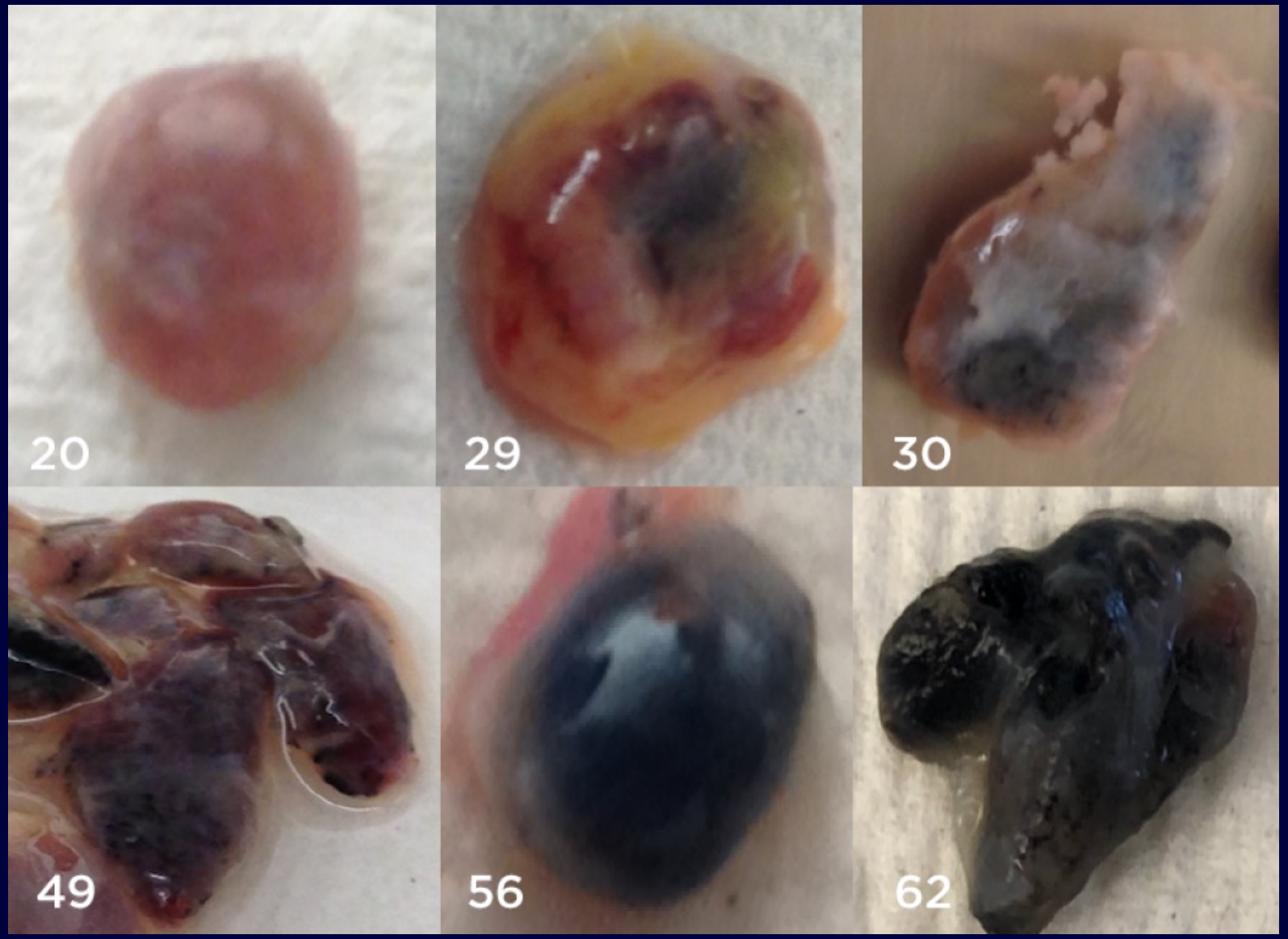
*The city with the highest level of air pollution (indicated by the level of fine particles) was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. CI denotes confidence interval. Rates have been adjusted for age, sex, smoking, education, and body-mass index.

†The risk of death for a current smoker with approximately the average number of pack-years of smoking at enrollment (25 pack-years), as compared with that for a nonsmoker.

‡The risk of death for a former smoker with approximately the average number of pack-years of smoking at enrollment (20 pack-years), as compared with that for a nonsmoker.



Ana Paula Cremasco Takano et al. Environ Res. 2019 Jun;173:23-32.



Lung lymph nodes from six non-smokers with their age just in the bottom left of each image.
Image credit: Donna Farber / Columbia University Irving Medical Center.

Questions