Tobacco: Enemy of Mankind

Pharmacology

active substances in tobacco smoke
- nicotine,
- carcinogenic tars
- carbon monoxide.

Nicotine (1-Methyl-2-(3-pyridyl) pyrrolidine is a poisonous, volatile alkaloid derived from tobacco (*Nicotiana* spp). It can be used as an **insecticide and fumigant**

An average cigarette contains
- 0.8 g of tobacco
- 9 – 17 mg of nicotine of which 10% is absorbed

however the amount varies with the smoker and cigarette type.

Transpulmonary absorption depends on alveolar distribution and consequently only 10% of an inhaled dose reaches the systemic circulation

There is limited absorption in the stomach due to the acid contents present
(nicotine forms salts with most acids)

Rapid absorption of nicotine in the lungs allows peak plasma concentrations to occur whilst smoking the cigarette.
There is a rapid decline in the plasma concentrations after completing the cigarette
after 10 mins only 50% of the peak concentration is present in the plasma.

HALF-LIFE = 10min

In the natural form nicotine is **not well absorbed from the buccal mucosa** however nicotine in inhaled tobacco is applied to the buccal or nasal mucosa and **enters the circulation within se**conds causing
- an increase in heart rate,
- increase in ventricular stroke volume
- increase in myocardial oxygen consumption.

Nicotine in chewing gum is buffered to an alkaline pH
and so is mainly unionised and absorbed well across the mucosa.
Pipe or cigar smoke is less acidic than cigarette smoke
and the nicotine is absorbed from the mouth and nasopharynx rather than the lungs.

Nicotine patches applied for 24 hrs cause the plasma concentrations to rise to 75-150 nmol/l over 6 hrs and remain constant for about 20 hrs.

Nicotine produces
- a sense of euphoria,
- heightened alertness,
- can enhance learning and memory
- promotes a sense of relaxation
- however it is **powerfully addictive**
- readily leading to habitation, tolerance and dependency.
- Nicotine is a **central nervous system stimulant** which may produce tremors and convulsions with very high concentrations
- It can also **stimulate respiration** by directly affecting the medulla and by activating the peripheral chemoreceptors in the carotid body and aortic arch.
- In small doses it stimulates and in large doses depresses the autonomic ganglia and myoneural junctions. .

People who smoke for the first time feel nauseous and can vomit because of the stimulation of the sensory receptors in the stomach. This response declines with repeated doses

- **The principle urinary metabolite is cotinine and this is due to the liver metabolism of nicotine**

Nicotine and its metabolites are excreted in urine and in breast milk.

The withdrawal of nicotine causes

- restlessness,
- irritability,
- aggressiveness
- anxiety,
- difficulty concentrating
- impaired psychomotor tasks,
- sleep disturbance.
- AND it produces cravings.

CELLULAR PHARMACOLOGY

At the cell level **nicotine acts on the nicotinic acetylcholine receptors (nAChR) in autonomic ganglia, adrenal medulla and in the neuromuscular junction**.

Nicotine opens cation channels causing neuronal excitation and can cross the blood brain barrier.
chronic nicotine use causes an increase in the number of (nAChR) which may represent an adaptive response to prolonged receptor desensitisation.

There is likely a balance between activation of (nAChR) causing neuronal excitation and desensitisation causing synaptic block.

Nicotine has the same effect on muscle fibres as acetylcholine however nicotine is not destroyed by cholinesterase or is destroyed so slowly that the action persists for many minutes to several hours.

Nicotine causes localised areas of depolarisation of the muscle fibre membrane at the motor end plate where the acetylcholine receptors are located. Then when the muscle fibre recovers from a previous contraction the depolarised areas with their leaking contractions causes new action potential which causes a state of muscle spasms. **i.e THE MUSCLE CONTINUES TO THINK ITS BEING STIMULATED**

The peripheral effects of small doses of nicotine result from the stimulation of the autonomic ganglia and peripheral sensory receptors mainly in the heart and lung. The stimulation of these receptors elicits various autonomic responses including tachycardia, increased cardiac output and increased arterial pressure and a reduction in gastrointestinal motility and sweating. These responses decline with repeated doses although the central affects remain.

Nicotine stimulates postganglionic neurons in the same manner as acetylcholine because the membranes of the neurons have nicotinic type acetylcholine receptors. This is why drugs that cause autonomic effects by stimulating the postganglionic neurons are called nicotinic drugs.
Nicotine excites sympathetic and parasympathetic postganglionic neurones at the same time resulting in
a strong sympathetic vasoconstriction in abdominal organs and limbs
but at the same time resulting in **parasympathetic effects such as increased gastrointestinal activity and sometimes slowing of the heart.**

Nicotine inhibits spinal reflexes causing skeletal muscle relaxation. This is probably due to stimulation of the inhibitory Renshaw cells in the ventral horn of the spinal cord. Smoking also appears to wake up people when they are drowsy and calms them down when tense.
Studies show that small doses of nicotine cause arousal but large doses do the reverse.
Smoking does not reduce anger but can reduce performance in logical thought processes.

Nicotine also stimulates antidiuretic (ADH or vasopressin) release which increases the permeability of the distal tubules and the collecting ducts of the kidney to water.
This allows a large amount of water to be reabsorbed and decreases urine volume but does not markedly alter the rate of renal excretion of solutes.

Smokers tend to weigh less than non-smokers because of reduced food intake and so cessation of smoking causes a weight gain.

Nicotine constricts the terminal bronchioles of the lungs which increases the resistance of airflow into and out of the lungs.
Nicotine paralyses the cilia of the respiratory epithelia allowing debris accumulation to occur causing further problems in breathing.
The smoke from cigarettes has an **irritating effect which causes**

- **increased fluid secretion into the bronchial tree**
- **swelling of the epithelial lining.**

A light cigarette smoker will feel respiratory strain during maximal exercise and can have an impairment of performance from the respiratory effects of smoking.
Few chronic smokers do not develop any degree of emphysema.
In emphysema there is

- chronic bronchitis,
- obstruction of many terminal bronchioles
- destruction of many alveolar walls.

In severe emphysema as much as 4/5ths of the respiratory membrane can be destroyed and slight exercise can cause respiratory distress.

Tolerance and dependence:
The effects of nicotine associated with peripheral ganglionic stimulation show rapid tolerance (perhaps due to desensitisation of nicotinic nAChR by nicotine. Large doses of nicotine produce a block of ganglionic transmission rather than stimulation.
Tolerance to the central effects of nicotine (e.g. in the arousal response) is less than in the periphery.

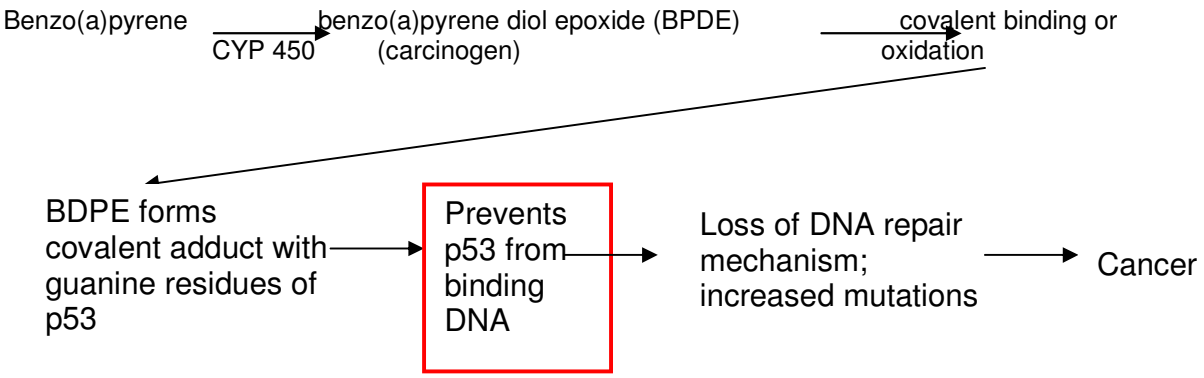
Nicotine is addictive and produces excitation of the mesolimbic pathway and **increased dopamine release in the nucleus accumbens**. A physical withdrawal syndrome occurs in people used to regular nicotine administration.

The withdrawal syndrome is less than for opiates and can be alleviated by amphetamines as well as nicotine.
The nicotine withdrawal syndrome lasts 2 – 3 weeks though the **craving for cigarettes persists**.
Relapses in cessation of smoking occur once the physical withdrawal syndrome has ceased.

Pharmacological treatment of nicotine dependence:
The most successful cure for smoking combines psychological and pharmacological treatment.
The most common pharmacological approach is **nicotine replacement** which relieves the withdrawal syndrome. Nicotine is short acting so chewing gum can be used several times per day or a transdermal patch is applied daily. These preparations can cause nausea, gastrointestinal cramps, cough, insomnia and muscle pains. Nicotine is not used in patients with heart disease because of the risk of coronary spasm. Patches can cause local irritation and itching.

Clonidine a $\alpha_2$adrenoceptor agonist can reduce the withdrawal effects of nicotine as well as opioids and cocaine. It can be given orally or as a transdermal patch and is as effective as nicotine replacement. The side effects include hypotension, dry mouth and drowsiness.

METABOLIC PATHWAY OF A GIVEN CARCINOGEN



The DNA adducts induced by BPDE or nitrosamines can be repaired by the nucleotide excision repair pathway in human cells. …Normally, while p53 is present.

PATHOLOGY OF SMOKING

Association of cancer and cigarette smoking is a DOSE-DEPENDENT RELATIONSHIP

CARCINOGENS: over 50 different types in tobacco smoke

These carcinogens are metabolically active or can be **made metabolically active by CYP 450.**

Polycyclic Aromatic Hydrocarbons:

- can get into the blood stream

Formaldehyde and Nitrogen Oxides

- cause damage to the Mucociliary Escalator, **paralysing cilia.**

MACROSCOPIC CHANGES:

- Macrophages attempt to remove carbon particles, therefore

Hilar lymph nodes infested with carbon particles

HISTOLOGICAL SUBTYPES OF LUNG CANCER

SQUAMOUS CELL CARCINOMA – well differentiated. MALES > FEMALES

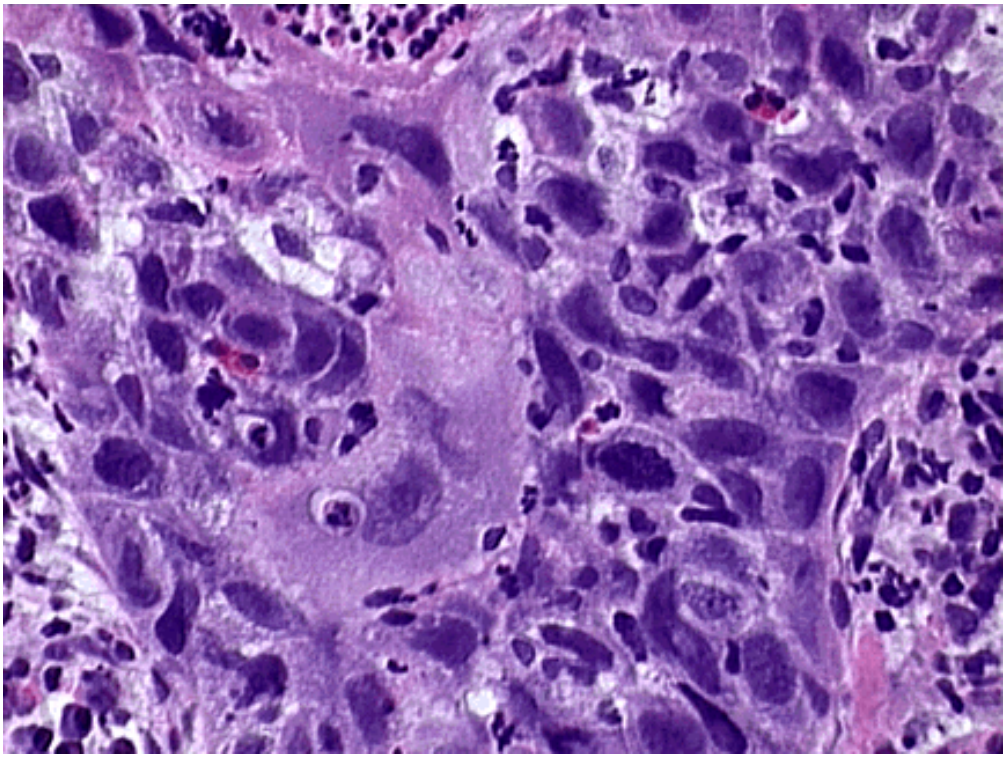
Centrally located and relatively slow growing.
Symptoms of obstruction and blocking.
Spread locally before they metastasise.
Epithelium changes into **STRATIFIED SQUAMOUS EPITHELIUM**
(this is METAPLASIA)

Cells exhibit

- **Pleomorphism** (very different in appearance)
- **Keratin Production** which should not happen in a healthy lung

!! CHARACTERISTIC !!
of Squamous Cell carcinoma

Following this, the cells go into ATYPICAL METAPLASIA
Then, DYSPLASIA (! A carcinoma in situ)
Here, cells exhibit TRIPOLAR MITOSIS (!!! THREE cells every mitosis)
After this stage the carcinoma becomes invasive and metastatic.



Squamous Carcinoma of Lung ← (High Power)

- This high power view centers on a neoplastic group of squamous cells.
- cells show much darker hyperchromasia of the nucleus, often with irregular nuclear outlines.
- intercellular bridges, caused by the retraction of the cytoplasm with fixation.
- The intercellular bridges are formed by **desmosomes.**
- The presence of bridges permits the categorization of non-keratinizing lesions as **squamous.**

- They grow in a stratified or pseudoductal arrangement, the cells have an **epithelial pearl formation with individual cell keratinization**. These tumours deposit keratin, and as they grow develop a necrotic, keratinous mass which appears cheesy on dissection

Overall five year survival 10%

SMALL CELL CARCINOMA:

… composed of …SMALL CELLS

USUALLY centrally located (hilar)

(small because they don't wait until an appropriate size before they divide)

ALMOST COMPLETELY UNDIFFERENTIATED (ANAPLASTIC)

! these tumor cells may produce ectopic adrenocorticotropic hormone (ACTH), resulting in Cushing's syndrome

EARLY METASTASIS ➔ Haematogenously

Thus, Small Cell Carcinoma is classified only as LIMITED (30%) or EXTENSIVE (70%)

Limited stage is confined to **one hemithorax** and regional lymph nodes

Microscopic features:

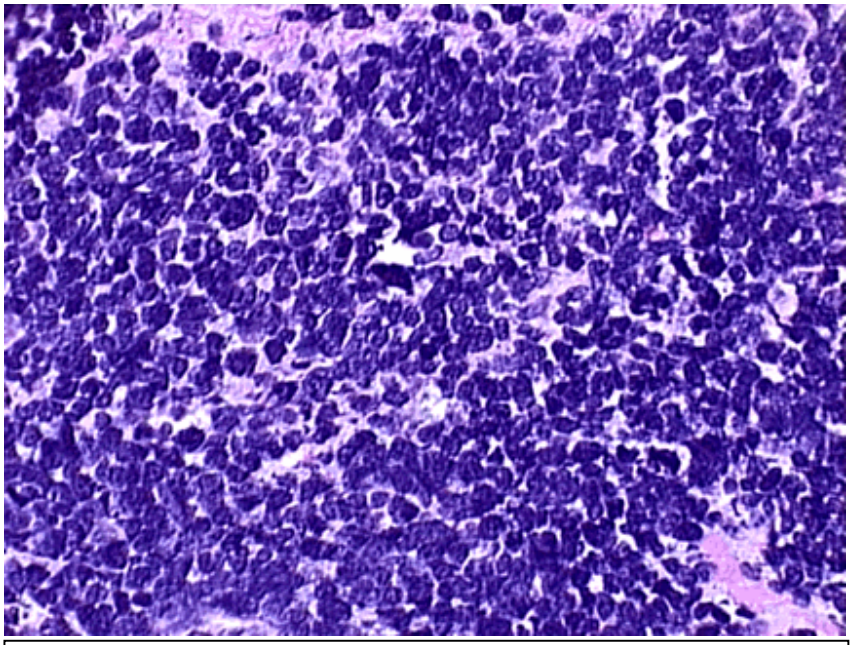
- sheets of uniform cells separated by thin strands of connective tissue
- Zones of necrosis are typically present in the center
- The cells are very hyperchromatic-appearing owing to the tightly packed small cells with scanty cytoplasm
- Individual cells vary in shape from ovoid to fusiform
- The cells of small cell carcinoma bear a superficial similarity to normal lymphocytes.
- However, small cell carcinoma nuclei are about twice the size of normal lymphocyte nuclei.
- The nuclei are generally molded to the shape of the cell and show dense homogenous chromatin and nucleoli are difficult to identify.
- These cells tend to be fragile and often show "crush artifact."

Macroscopic features:

- Over 90% are found in a central location.
- typically white-gray, soft and bulky with areas hemorrhage and necrosis.
- Commonly they grow around major bronchi

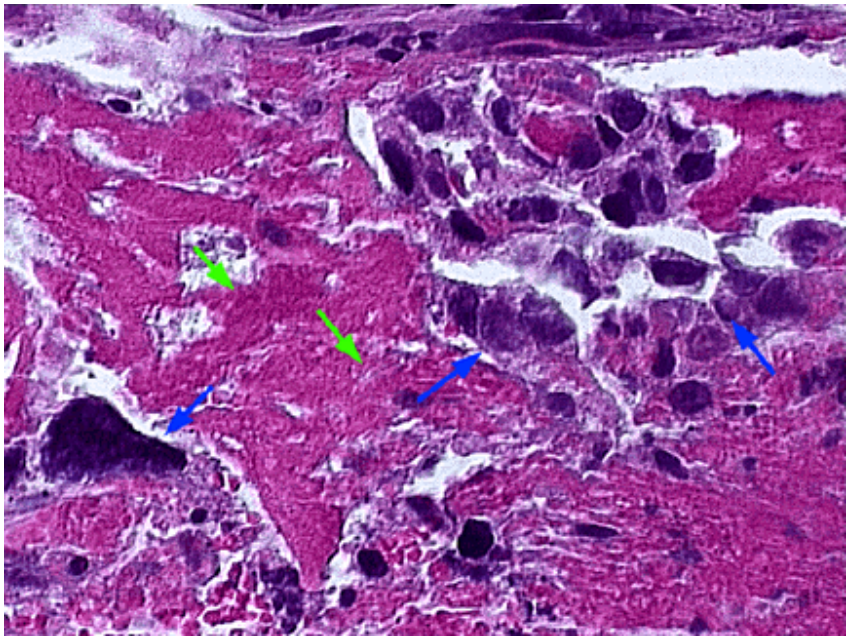
AKA . "Oat Cell Carcinoma"

Overall two year survival 25%



ABOVE: Small Cell Carcinoma of Lung (High Power)
• At this high power it is clear that there is no architectural arrangement for these malignant cells.
• In addition they lack cytoplasm.
• Frequently nuclei are so closely apposed that they appear to "mold".

BELOW: Large Cell Carcinoma of Lung (Med Power)
• The blue arrows point to typical examples of neoplastic cells.
• The green arrows demonstrate the necrotic debris.
• No gland formation or intercellular bridges



Large Cell Carcinoma:

* More frequent in males; Overall survival = 10% after 5 yrs

May be central or peripheral. The normal parenchyma is replaced by dense fibrous connective tissue containing nests of neoplastic cells.

Large cells with round to oval nuclei, prominent nucleoli and hyperchromasia

• Mucin negative by mucicarmine staining
• No intercellular bridges seen
• Ultrastructural evidence may support diagnosis of either adenocarcinoma or squamous carcinoma

Adenocarcinoma

Adenocarcinomas arise peripherally from mucous glands and the cells retain some of the tubular, acinar or papillary differentiation and mucus production.

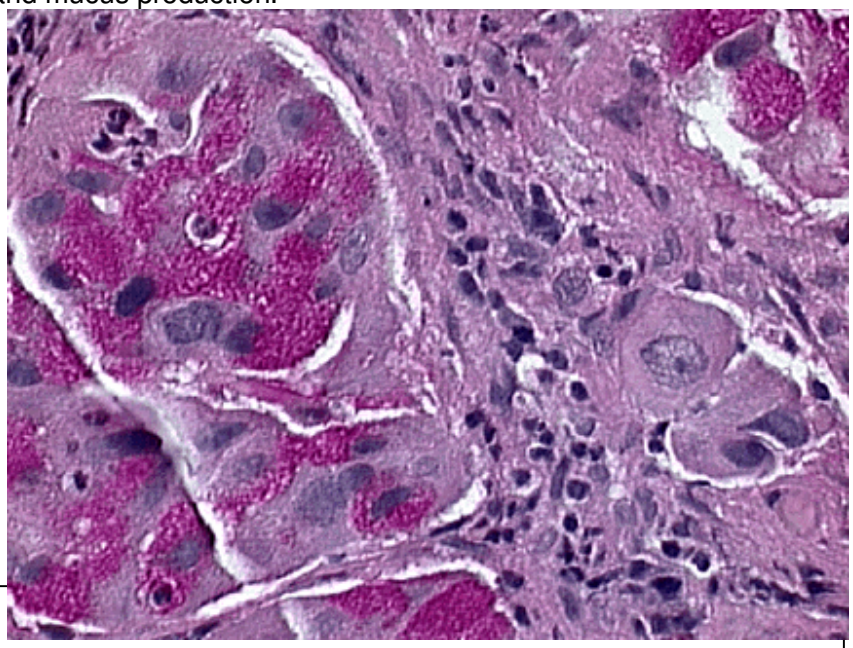
- Male incidence same as Female.
- now it is seen mainly in smokers.
- **More often peripheral**, asymptomatic
- spreads HAEMATOGENOUSLY.
- Becoming increasingly common.

Macroscopic:

May involve the pleura causing puckering and scarring.
• May be associated with pleural effusion
• Cut surfaces often glisten and are yellow if abundant mucin secretion within the tumor

Microscopic:

Usual bronchial adenocarcinoma is **gland forming**
• **Mucus secretion** may require special stains such as mucicarmine or PAS
• **Cells show large nuclei with prominent nucleoli**



Adenocarcinoma of Lung → (Mucin Stain)
• This is a view of a mucicarmine stain on an adenocarcinoma of the lung.
• The magenta granular staining seen in most neoplastic cells is mucin.
• This finding must result in a diagnosis of adenocarcinoma, which in this case is poorly differentiated.

EPIDEMIOLOGY + PRESENTATION OF LUNG CANCER

- **Squamous 34%**
  Large Cell 28%
  Adenocarcinoma and Bronchoalveolar 20%
  Small Cell 17%
  Mixed 1%

There is an IMMEDIATE BENEFIT to quitting:
The risk of carcinogenesis stops dead at the moment of cessation; otherwise it grows steadily.

clinical presentation*:* patient may have no signs

Other Cancers associated with tobacco smoke :
larynx,
oropharynx
nasopharynx
hypopharynx,
oesophagus,
bladder, renal pelvis
pancreas
Stomach,
renal body,
liver,
myeloid leukaemia.

- ***cough*** (80% of cases) due to infection distal to airway blocked by tumour
- ***haemoptysis*** (70% of cases) due to ulceration of tumour in bronchus
- ***dyspnoea*** (60% of cases) due to local extension of tumour
- ***chest pain*** (40% of cases) due to involvement of pleura and chest wall
- ***wheeze*** (15% of cases) due to narrowing of airway
- ***non-specific systemic signs:*** **weight loss, anorexia, malaise**
- signs on examination may include:
  - lobar collapse or volume loss
  - pneumonia
  - pleural effusion
  - fixed inspiratory wheeze
  - tender ribs (secondary deposits of tumour in ribs)
  - mediastinal compression including signs of nerve involvement
  - supraclavicular or axillary lymphadenopathy
  - clubbing

Oral + Oesophageal Cancers:

Usually SCC.
Most commonly pipe and cigar smokers.
Poor survival, less than 30% after 5 yrs.
DUE TO SOLUBILITY OF CARCINOGENS IN SALIVA

Stomach cancers:

Peptic Ulcers most common with smokers (actually IN THE DUODENUM, not stomach)
→Stomach = continuous war between **pepsin and acid** versus mucosal resistance.
Mucosal resistance depends on the following factors:

- Mucus production ⟸ **Helicobacter Pylori**
- Epithelial integrity
- Epithelial ability to regenerate (constant turnover)
- Bicarbonate produced to neutralise
- Good epithelial circulation to nourish the dividing cells ⟸ **SMOKING**

Studies have also identified **promoting agents**, non mutagenic agents responsible for promotion of the development of cancer after the carcinogen has been introduced. Promoting agents depend on their effects on cell replication. Sequence of carcinogen followed by promoting agent application is critical.

Carcinogens can be inactivated by:

- Conjugation to glutathione by glutathione S-transferase
- Epoxide hydrolases and aryl hydrocarbon hydroxylases (BPDE).
- Detoxification by conjugation to glucuronate and excreted
- Acetylation

Chemopreventive agents:

- **Phynethyl isothiocyanate** (cruciferous vegetables)- protects against nitrosamines
- **N-acetyl-L-cysteine** – nucleophilic and anti oxidant properties, precursor of glutathione
- **Retinoid, isotretinoin** – inhibit formation of secondary tumours
- **Dietary carotenoids** - anti oxidant
- **Vit A.-** anti oxidant

Cochrane review of retinol and carotiniod pharmacologic supplementation for those with risk of lung caner has shown that there is a statistically significant increase in the risk of lung cancer in those who take retinol and beta carotene vitamins to reduce lung caner.

'There is currently **no evidence to support recommending vitamins** such as alpha-tocopherol, beta-carotene or retinol, alone or in combination, to prevent lung cancer. A harmful effect was found for beta-carotene with retinol at pharmacological doses in people with risk factors for lung cancer (smoking and/or occupational exposure to asbestos). More research from larger trials and with longer follow-up is needed to analyse the effectiveness of other supplements.'

EMPHYSEMA (the emphysematous process is one of loss of lung parenchyma, not fibrosis)

= is the destruction of COLLAGEN and ELASTIN FRAMEWORK in the alveoli
→ RESULTS in **MASSIVE DEAD AIRSPACES**; **Plus LOSS OF RECOIL = NARROWED AIRWAYS**

PATHOLOGY:

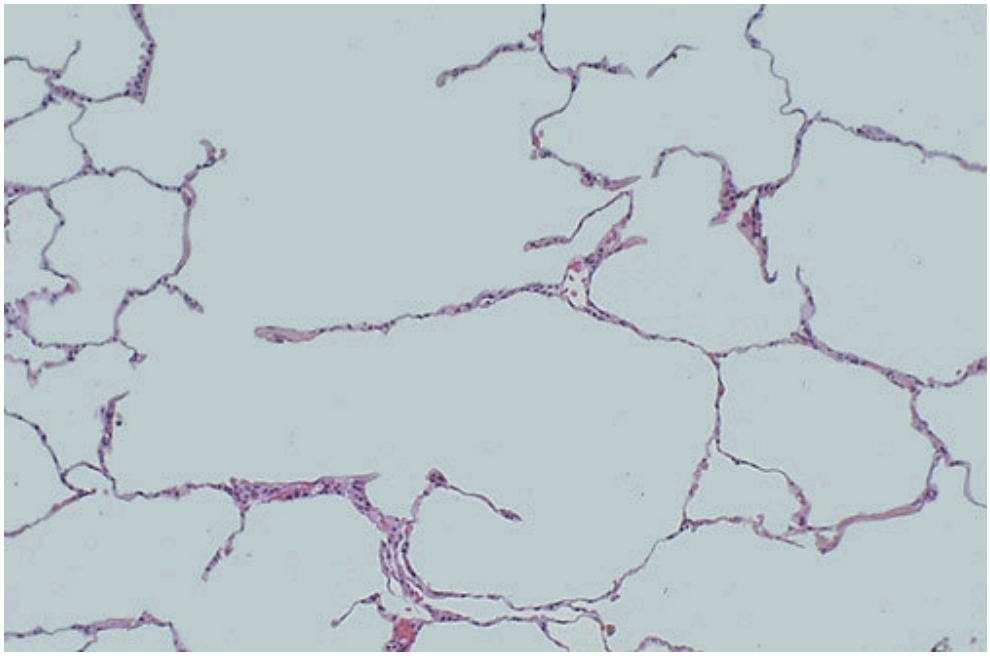
- **is in essence an Inflammatory response gone wrong.**
- **COLLAGENASE and ELASTASE** are produced by neutrophils and macrophages as they attempt to diapedese through the basal lamina of alveolar walls.
- **Death of neutrophils** results in further release (this time uncontrolled) of elastase.
- **NORMALLY α-1-Antitrypsin inhibits elastase!**
  - **BUT: in individuals with a genetic homozygous lack of alpha-1-antitrypsin (0.01% of population)**

  …THE ELASTASE IS UNREGULATED and thus DESTRUCTION IS WIDESPREAD

  This predisposes such individuals to emphysema.

HOWEVER: TOBACCO SMOKE INHIBITS Alpha-1-Antitrypsin; THEREFORE → EMPHYSEMA.
(this occurs only for neutrophils; somehow macrophage elastase is all-powerful and uninhibitable)

EMPHYSEMA FROM SMOKING IS SPECIFICALLY DIFFUSE,
occurs in the **centre of acinus** and not all over the acinus as in antitrypsin deficiency.
PREDOMINANTLY THE UPPER LOBE is involved. (with anitrypsin deficiency, it is the LOWER LOBE)



←Microscopically at high magnification, the loss of alveolar walls with emphysema is demonstrated. Remaining airspaces are dilated.

Side note:
Smokers cough is due to:
- Chronic bronchitis
- Infections, to which smokers are especially predisposed;
- Goblet cell metaplasia (thus much more mucous is produced)
- Left sided heart failure resulting in transudation of plasma into the alveoli
- ALL THIS irritates the parenchymal and bronchial chemoreceptors

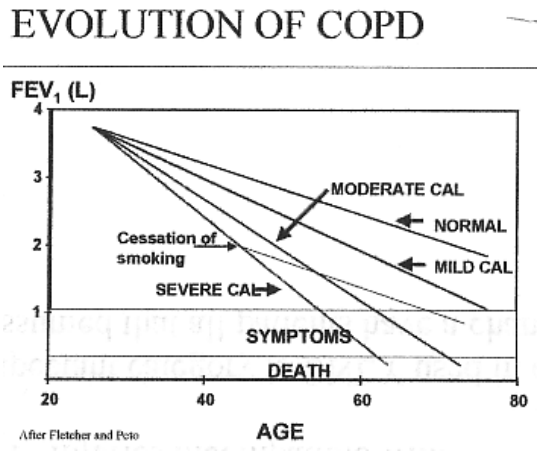
Chronic Obstructive Pulmonary Disease

…is defined as:
" A disease characterised by airflow limitation that is not completely reversible"
The airflow limitation is:
both PROGRESSIVE and
associated with an ABNORMAL INFLAMMATORY RESPONSE to irritants
Thus, in relation to smoking, its **mainly chronic bronchitis and emphysema.**

CHRONIC BRONCHITIS:
- **Productive cough on MOST DAYS**
- **for at least 3 CONSECUTIVE MONTHS**
- **over no less than 2 CONSECUTIVE YEARS**

Pathologically, it is neutrophilic inflamation in LARGE AIRWAYS.
Neutrophil elastase is a POTENT SECRETAGOGUE (i.e it promotes secretion)
THUS: bronchial mucus glands hyperproliferate

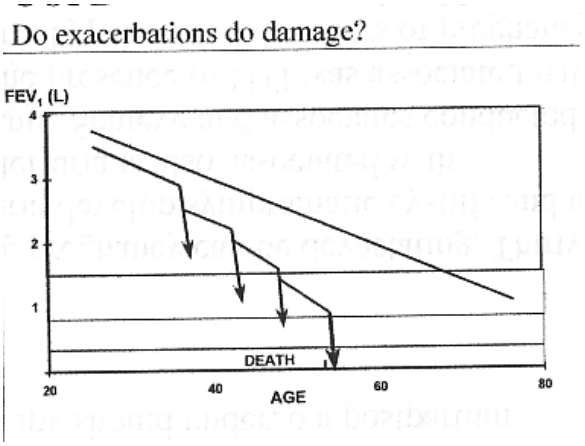
THIS MAY LEAD TO:
- **Bronchiolitis (inflammation of smaller airways)**
- **Airway fibrosis**
- **Smooth muscle hypertrophy**
- **Lumen occlusion by mucus plugs**



Adaptation to COPD
= dynamic hyperinflation
(attempts to hyperinflate the lung to compensate for loss of recoil)
= limited adaptive capacity;
because **higher lung volumes are less efficient for respiratory muscles**
Also causes discomfort and fatigue

Epidemiology of COPD

All smokers have bronchiolitis to some degree.
15-20% will develop COPD.
SLOW ONSET: **takes 30yrs**
SMOKING IS THE CAUSE: not just a trigger



Acute Exacerbations

Increased sputum volume and purulence
Together with
Increased Dyspnoea
(excluding other possible causes of dyspnoea,
eg. pulmonary embolism and heart failure)
can be caused by superimposed bacterial infection.

BEHAVIOURAL SCIENCES

QUITTING: the Elements of Dependence

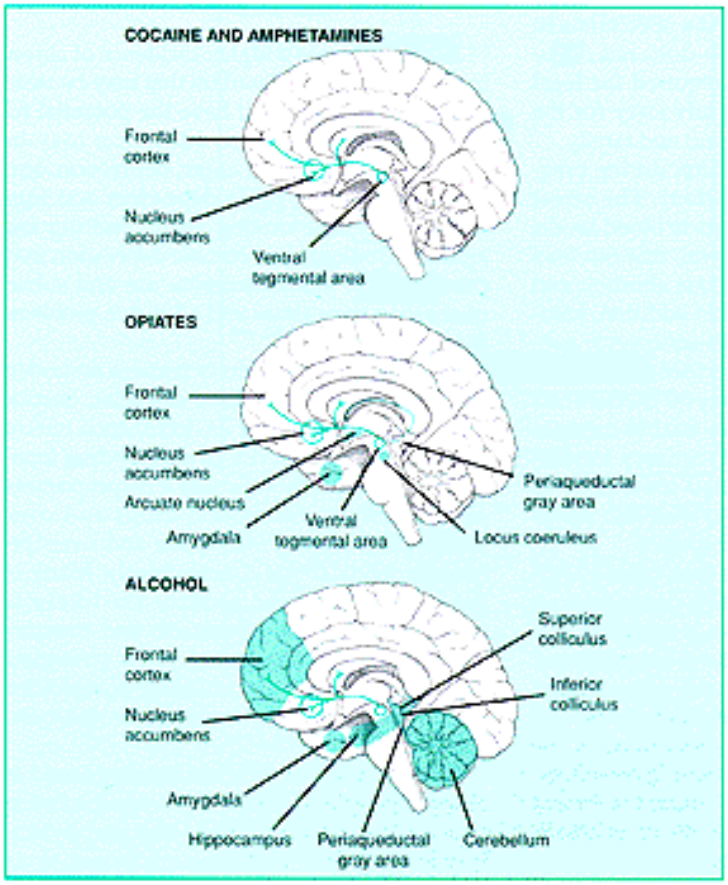
NICOTINE ALONE WILL NOT CAUSE ADDICTION:

Need all the elements,

- Context
- Ritual
- Sensory Inputs
- Nicotine stimulus

Responsibility rests with the REWARD CENTRE

Reward Pathways in the Brain. →
Animal studies suggest the existence of at least one central reward-reinforcement pathway for drug self-administration in the human brain. The stimulant-reward system *(top)* directly influences the neurons using dopamine that connect from the ventral tegmental area (VTA) to the nucleus accumbens (NA) and thereafter to the frontal cortex. The opioid system *(middle)* appears to involve structures such as the periaqueductal gray area, arcuate nucleus, amygdala and locus coeruleus, which use peptides that mimic the action of drugs such as heroin and morphine and indirectly influence the NA in a manner similar to that of stimulants. Alcohol and other sedative-hypnotics *(bottom)* also indirectly affect the VTA-NA reward system. This effect is mediated by GABA receptors, which are distributed widely and which influence the central dopaminergic reward system through mechanisms that include opioid pathways.



WITH NICOTINE ADDICTION, the REWARD THRSHOLD IS
INCREASED
Thus → withdrawal.

CESSATION STRATEGIES:

1. **Willpower:** 2% success
2. **Advice from Physician:** adds 2% absolute chance to any other measure
3. **Pharmacotherapy:** NRT (Nicotine Replacement Tx) aim is to eliminate nicotine concentration troughs
   8 weeks of patches is apparently the best method
   combination patch/gum/inhaler/ is less successful
   BUPROPION doubles chances (= is an SSRI antidepressant with limited applications in tmt of depression)

The RELAPSE RATE for cessation is depressing, approx. 50% after 1 year.

TOTAL OPTIMUM SUCCESS RATE = 15 to 20%

Sigmund Freud tried to give up smoking for 43 years, until he died of cancer at 83.