Exposition à la fumée passive de l'enfant : de l'épidémiologie à la biologie

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1. History of cigarette smoke
2. Tobacco toxicants
3. Passive smoke: developmental and epidemiological data
4. Pathogenicity of passive smoke

Active smoke
When did we know?

- 1898: *Rattmann* (medical student from Wilzburg)
- 1930: *Muller (autopsy association with lung cancer Zeitschrift for Krebsforschung)*
- 1950's: First american and british publications (lung cancer*: JAMA & BMJ,* ciliary anomalies: *NEJM*)
- 1954: Cancer Society National Board → smoke causes lung cancer

1960 ⟹ 45% of the US doctors continue to smoke

And when did they know….?

- 1 ar ch s yi
- 1 a ncer a
- 1 pa a es
- 2

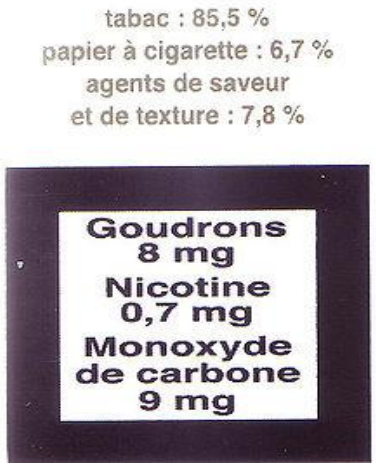
Cancer Epidemiology Biomakers and Prevention 2007

Tobacco consumption in Switzerland *(OFSP January 2013)*

Smokers	**24.8%,** (33% 2001), USA 15.2% en 2015
Smokers : 15 -19 years	22.5%
Smokers: 11-15 years:	10.5%, (2010)

1964 No publicity on radio and TV

2010 Cigarette box should contain warnings

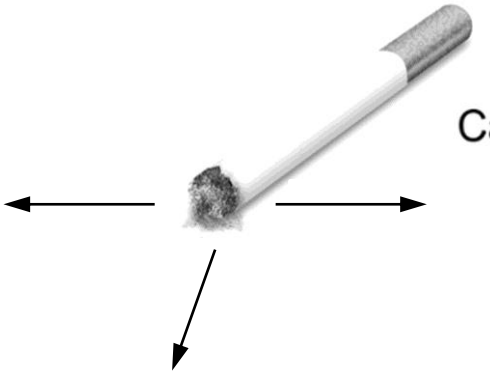


2. Tobacco toxicants

Tobacco smoke : 4000 chemical substances

- **Mutagenic, toxic, pro-inflammatory and immunosuppressive properties**
- Carcinogenic chemicals contain metals (Cd, Ni, Pd, Al)
- Toxins (immunomodulation and addiction)

Nicotine
Reactive oxygen species
Carbon monoxide
Acrolein
Others



Carcinogenic toxins

- Polycyclic aromatic hydrocarbons
- N-Nitrosamines
- Nickel
- Cadmium
- Chromium
- Arsenic
- Misc organic compounds
- Others

Toxins that are directly addictive or may enhance addiction

- Nicotine
- Acetaldehyde
- Ammonia
- Others

Adapted from Lee J et al. J Dent Res 2011

Environmental tobacco smoke (ETS)

Main stream smoke MS

Directly inhaled & shouldering tabacco:
Solid (particulate) and volatile (gas) phases

Side stream smoke SS

Exhaled : solid and volatile phases

Produced at lower temperature
Greater amounts of toxicants

Valvanidis, Int J Environ Res Public Health 2009

3. Passive smoke (second hand smoke, environmental tobacco smoke, ETS): developmental & epidemiological data

In children:

1. Direct effect of smoke compounds during pregnancy and lactation
2. Passive smoke exposure in the family house

Prevalence of passive smoke : depends on the countries,

Global youth tobacco survey 2007 (13-15 y.):

- 20-48% in Western Europe
- 40-97% in Eastern Europe and Central Asia
- 4 % Swiss children population *(OFSP 2012)*

Can be assessed by questionnaires or nicotine measurements of indoor air or cotinine (principal nicotine metabolite) bio-monitoring (blood, urine or saliva)

- Nicotine affinity : liver, brain,>kidney, spleen, lung> adipose tissue

In Switzerland 15-20% of the mothers are smokers (12% UK, 15% Australia)

80% of them will not stop smoking during pregnancy*

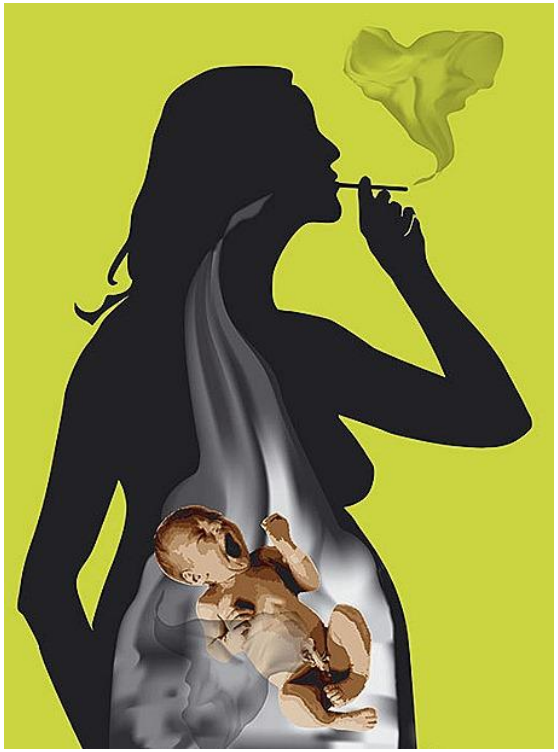
Many pathological outcomes:

Impaired fetal development

Low birth weight

Increased neonatal death

Priming for chronic pathologies (diabetes, asthma, hypertension)



*(Swiss federal Office of Statistics, 2007 last data report)

Prenatal (in utero) effect of smoking

Nicotine freely crosses the placenta

Increases placenta release of norepinephrine in maternal blood, reducing blood flow to placenta

Tobacco smoke increases CO fixing on maternal and fœtal Hb, reducing the quantity of O_2 delivered to the fetus

➡ « Small for date »

– Levels of nicotine reaching the fœtus similar or even higher than in the mothers *(foetus eliminate nicotine in the urine → aminiotic fluid and drinks it again)*

Lung epidemiological data of exposure to passive smoke in children

More 100 reviews published on this topic *(Meta-analysis Pediatrics 2012)*

- ✓ Increased wheezing, bronchial hyperreactivity, hospitalization, and asthma (pregnancy and childhood) OR 1.7 *(Chest 1976, Lancet 1982, Am Rev Resp Dis 1980)* *(Grade A)*
- ✓ Reduced pulmonary functions *(Tager, Am Rev Resp Dis 1993)*
  - Strong association between serum cotinine level and worse lung function at 6 years of age
- ✓ Increased Sudden Infant Death Syndrome (Altered respiratory control)
- ✓ Arrested lung growth and acclerated maturation (pregnancy)
- ✓ In almost all studies the effects were greater when babies were exposed pre-natally and post-natally

Identification of 79 prospective studies

Flowchart for identifying studies.

TABLE 1 Passive Smoke Exposure and Incidence of Wheeze

Smoking Exposure	Age the Outcome Was Collected	No. of Studies	Pooled OR	95% CIs	I^2, %	Ref. Nos.
Prenatal maternal	≤2	14	1.41	1.19–1.67	87.9	17;30;38–48
Maternal	≤2	4	1.70	1.24–2.35	0.0	17;38;46;49
Paternal	≤2	0				
Household	≤2	10	1.35	1.10–1.64	64.5	39;40;42;43;46;50–53
Prenatal maternal	3–4	8	1.28	1.14–1.44	65.6	17;28;38;42;54–57
Maternal	3–4	4	1.65	1.20–2.28	48.5	17;38;54;58
Paternal	3–4	0				
Household	3–4	4	1.06	0.88–1.27	54.5	42;55;56;59
Prenatal maternal	5–18	5	1.52	1.23–1.87	21.1	29;57;58;60;61
Maternal	5–18	3	1.18	0.99–1.40	1.40	62–64
Paternal	5–18	2	1.39	1.05–1.85	0.0	60;63
Household	5–18	5	1.32	1.12–1.56	1.7	57;63;65–67

- Increased risk of wheezing and /or for asthme by 30-70% , strongest effect with exposure to maternal smoke and household(passive smoke)

Pediatrics 2012, Meta-analysis

Interventional epidemiological data

- Introduction of smoke-free legislation implemented in England in 2007 was associated with decreased number of hospitalisations for respiratory tract infections by 10%.
  - Study of >1million hospitalisations between 2001 and 2012

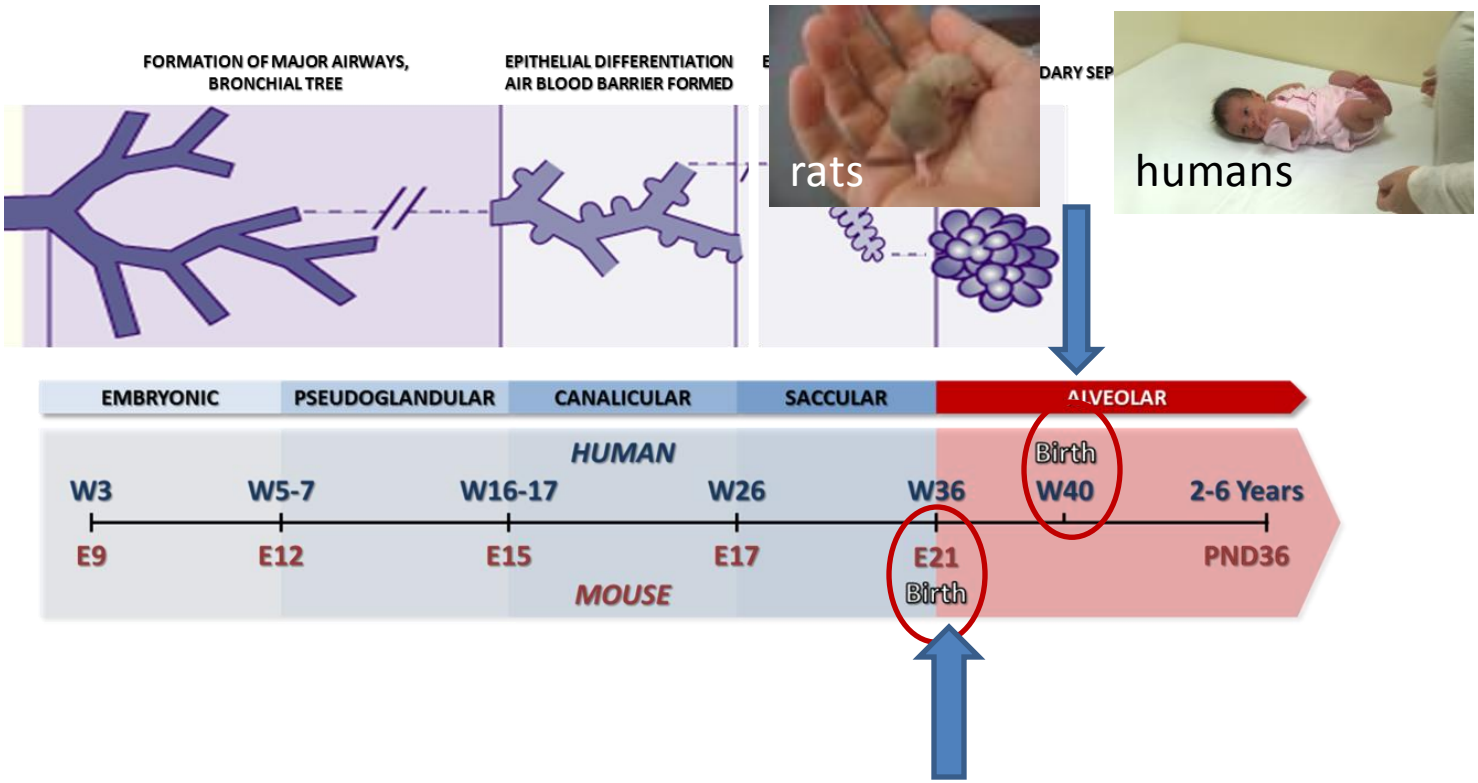
ERJ 2015 Been et al.

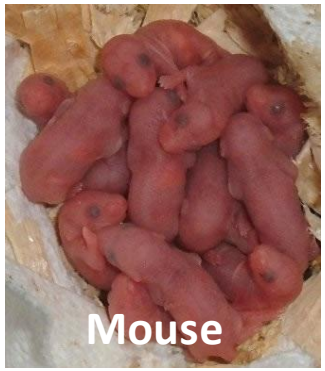
It is still unclear whether the long lasting effects are due to prenatal exposure or to post natal exposure (passive smoke) or both

4. Pathogenicity of passive smoke in lung development

- molecular and cellular basis

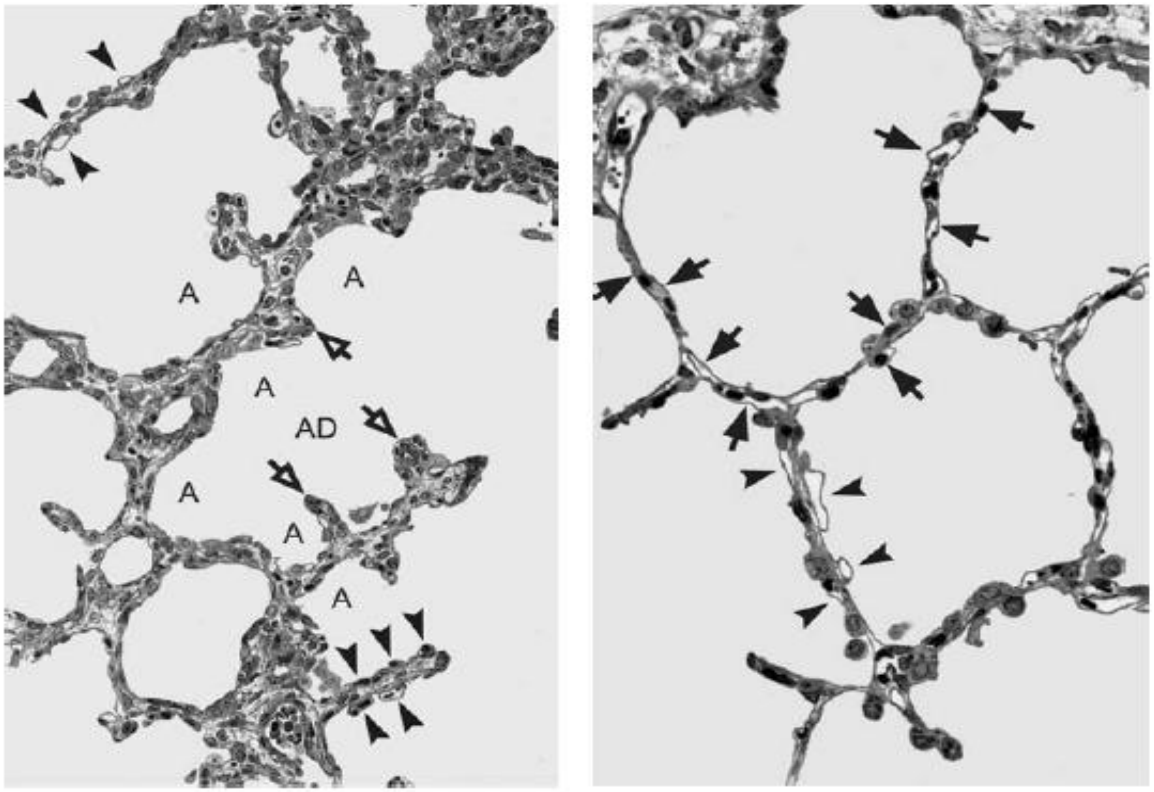
Lung development in mouse and human





In mouse the alveolarization occurs completely post-natally (PND2-PND36)

Alveolarization stage



Schittny and Burri, 2008, *Fishman's Pulmonary Diseases and Disorders*, 4th edition

1. Apoptosis
2. Proliferation
3. Differentiation
are tightly regulated for efficient gas exchange

Animal models for CS studies on lung development

CS exposure through a **smoking chamber**

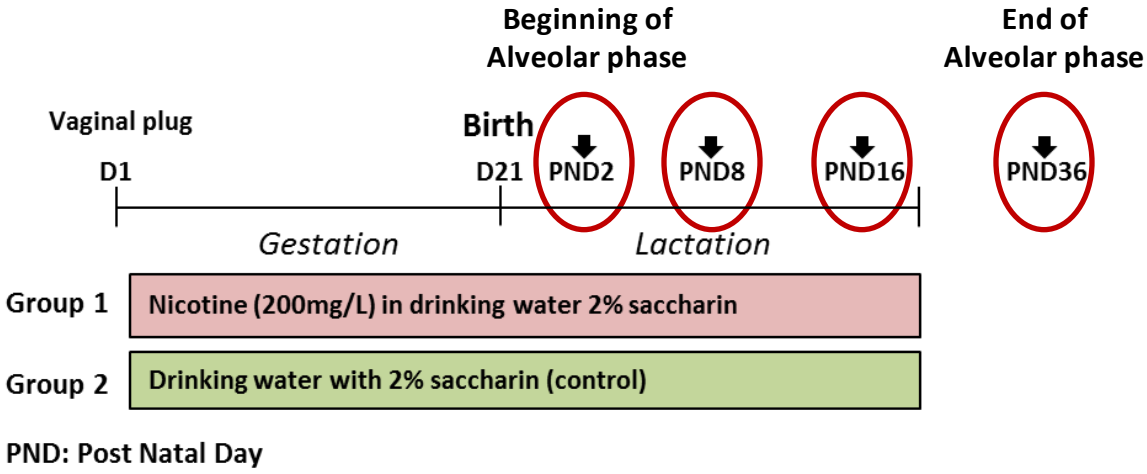
- ✓ Close to "real life"
- ✓ Include all the toxic compounds of a cigarette
- ✓ Expensive and complicate set-up

- **Nicotine** administration (oral, minipumps, IP) Main component of cigarette smoke (1-3 mg per cigarette) Addictive compound of tobacco

- ✓ Easier set-up
- ✓ Mimic some of the side effects of CS
- ✓ Useful to study Nicotine Replacement Therapies (patches, **e-cigarettes**)

Nicotine model

C57bl6 ♂ x C57bl6 ♀



→ Monitoring of cotinine levels in blood (medium smokers)

1. Investigate lung developmental alterations due to nicotine exposure *in utero* and during lactation

Are the effect of passive smoke or prenatal smoke related mainly to nicotine ?

Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring

Nafeesa N. Dhalwani, PhD[a,b], Lisa Szatkowski, PhD[a], Tim Coleman, MD[b], Linda Fiaschi, PhD[a], Laila J. Tata, PhD[a]

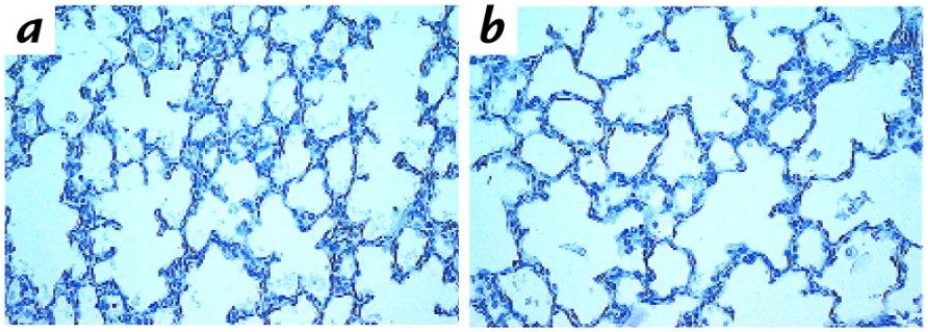
Pediatrics, May 2015, UK

Seems more toxic than smoking….,
trend to have more respiratory morbidities (asthma)

Effects of nicotine on **alveolar stage**

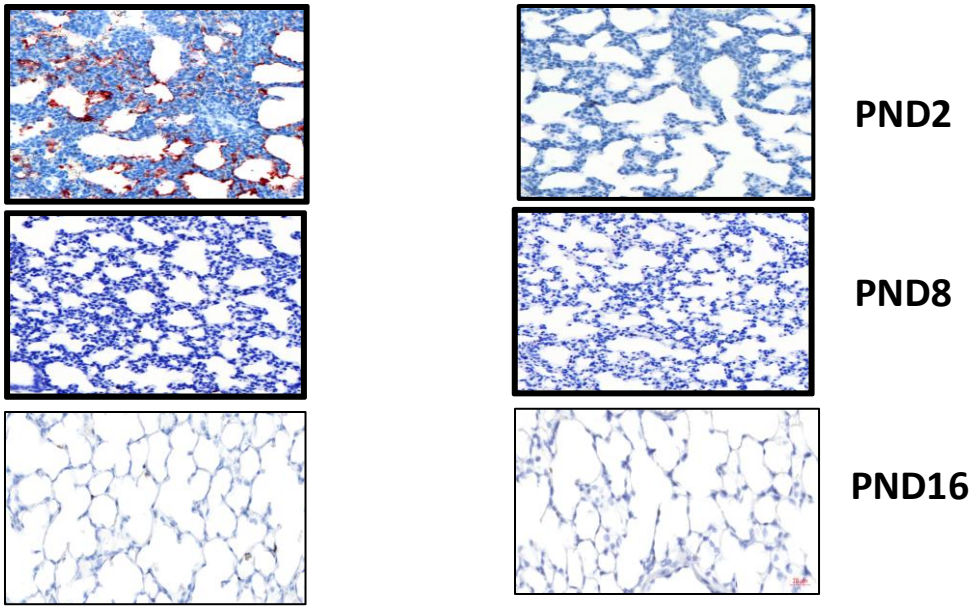
- Monkeys and rats: Enlarge alveolar space

Saccharin Nicotine

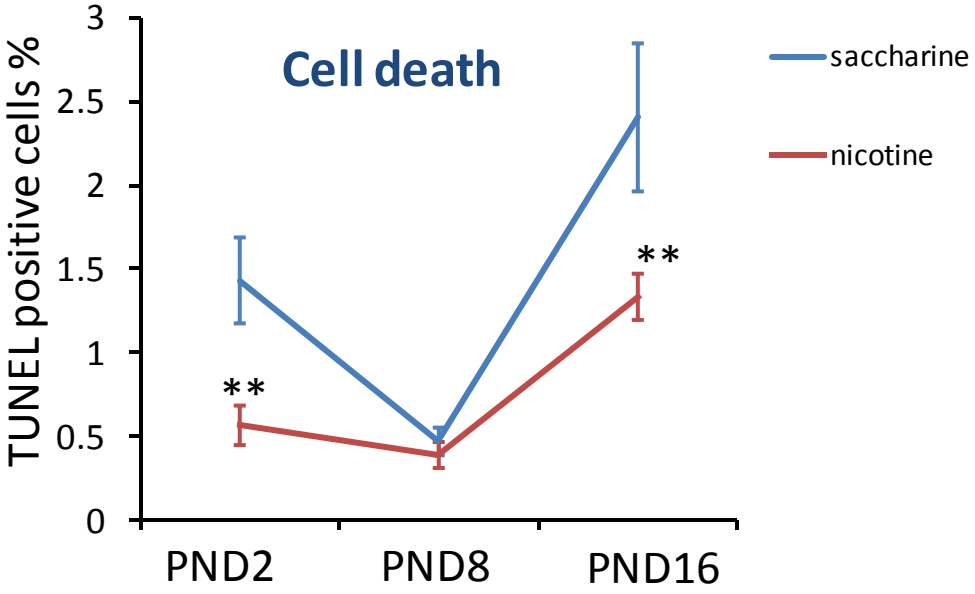


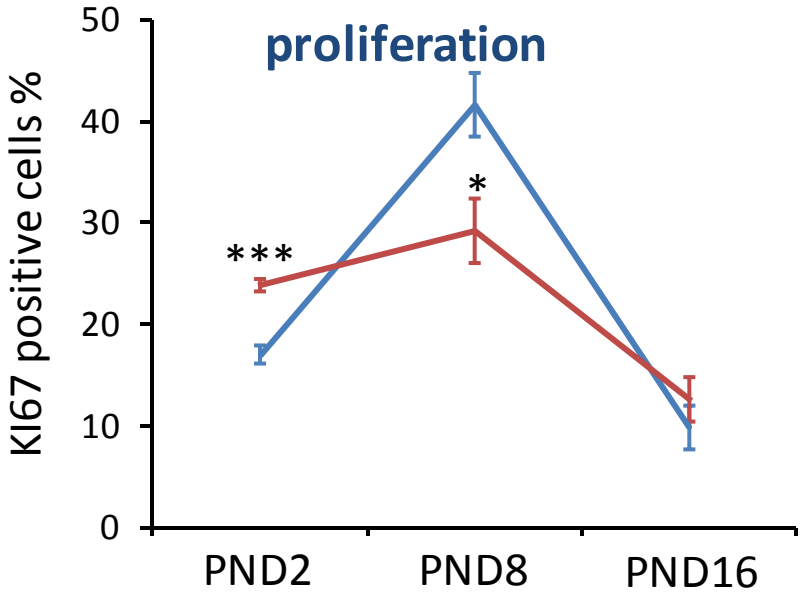
J CLIN INVEST 1999;103:637-647

- Mice: increased lung maturation
  But transient effect



Barazzone et al, unpublished





Nicotine affects proliferation and apoptosis dynamics during lung maturation

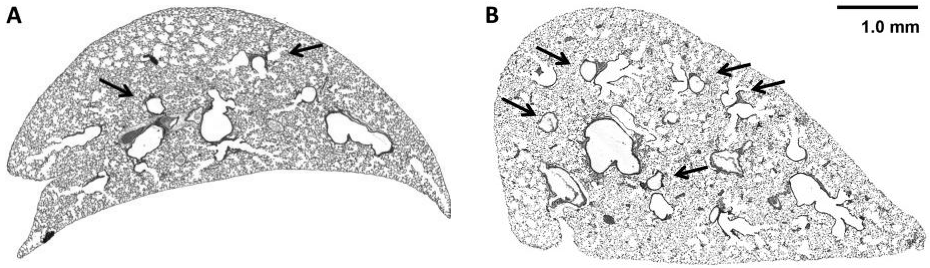
- Humans: ? Hypothesis:
- Acclerated lung development (alveoli and vessel)

    apoptosis for thininnig occurring at earlier time point?

→Less respiratory distress syndrome in premature infants of smoking mothers

Effects of nicotine on **airways growth**

decreased the diameter of proximal airways and accelerates the development of the bronchiolar part of the lungs in lambs

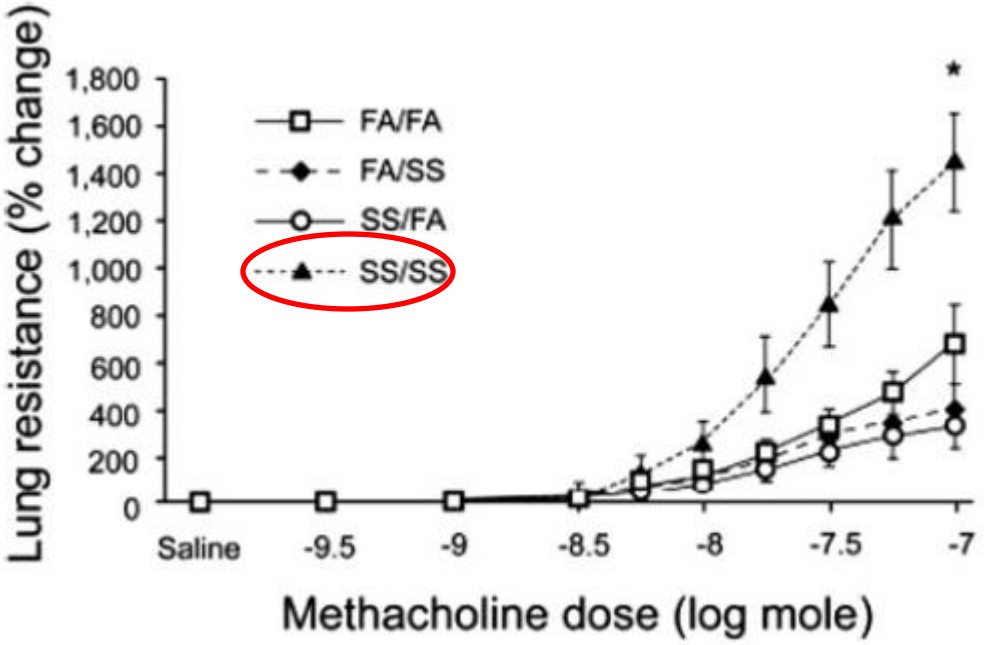


AM J RESPIR CELL MOL BIOL 2012;46:695-702

Alter lung geometry by increasing airways length and diminishing their diameter in mouse

Still contrasting results depending on the nicotine dose, animal model and way of administration

Lung resistance in **adult rats** exposed to Sidestream smoke during gestation and postnatally (until weaning)



FA: filtered air
SS: sidestream smoke

More pronounced effect when animals were exposed pre and postnatally

Nicotine

Anti apoptotic

Cancer

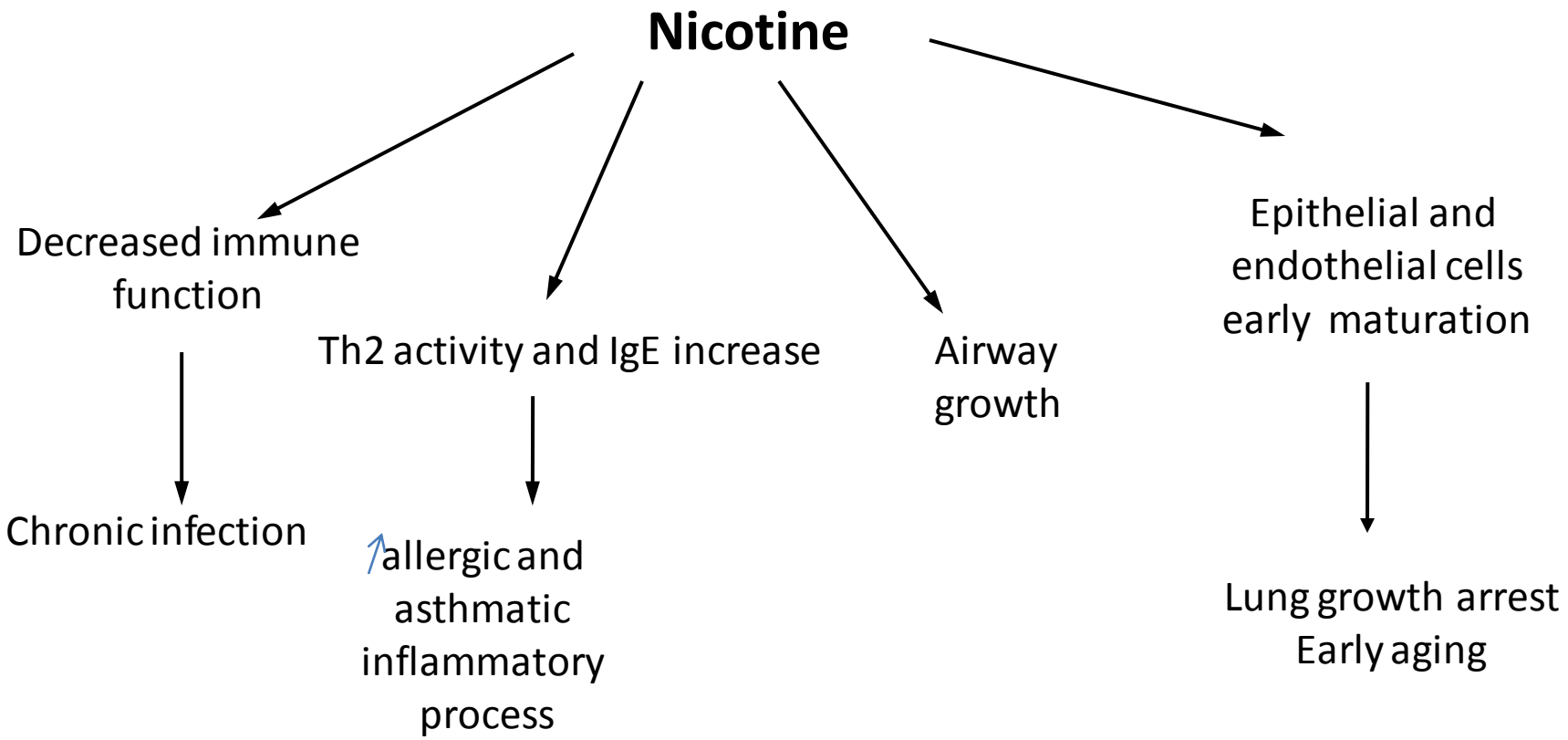
1-5% of the smokers will develop smoke-related malignancies

Pro apoptotic

COPD (~50% of the smokers), emphysema, ALI, Fibrosis (IPF)

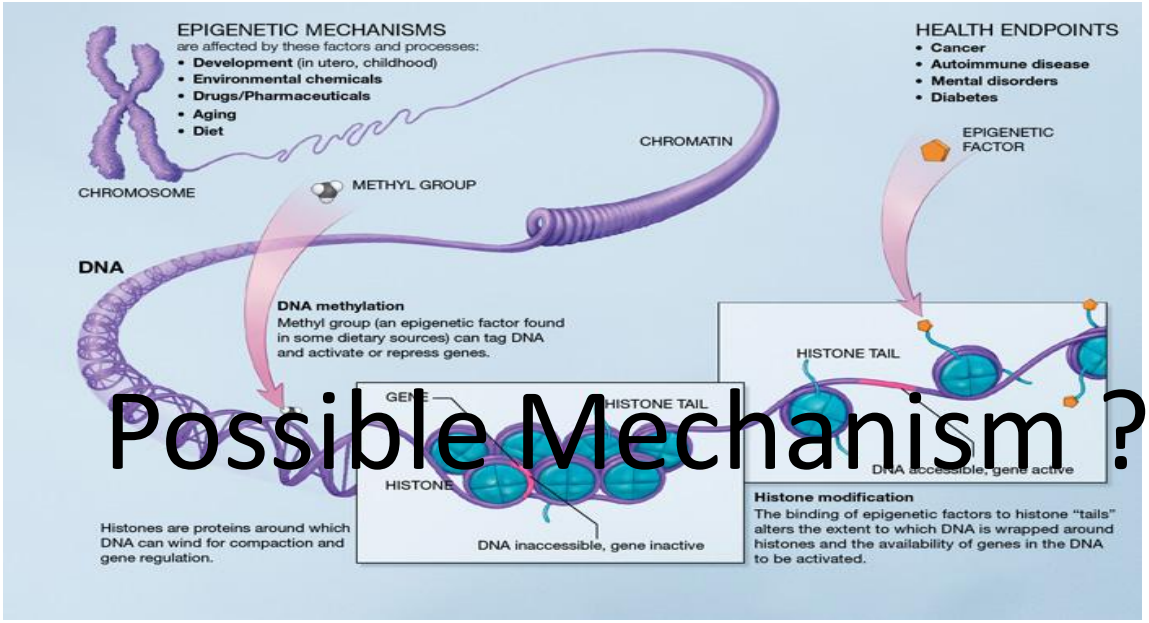
Lung development ?

Possible effects of nicotine on the lung



Adapted from Cheragui, Eur J Pediatr 2009

Epigenetic modification



Possible Mechanism ?

Change in gene expression without nucleotide sequence modification
by DNA methylation or acetylation or change in histones

Analysis of >600 DNA by buccal scrap of children (preschool age) and their mother
→changes in DNA methylation
GSTM1 (involved in metabolism of tobacco smoke)
AXL (gene promoting mitogenesis)

Am J Respir Crit Care Med 2009

Rehan *et al. BMC Medicine* 2012, **10**:129
http://www.biomedcentral.com/1741-7015/10/129

BMC Medicine

RESEARCH ARTICLE Open Access

Perinatal nicotine exposure induces asthma in second generation offspring

Virender K Rehan[1*], Jie Liu[1], Erum Naeem[1], Jia Tian[1], Reiko Sakurai[1], Kenny Kwong[1], Omid Akbari[2] and John S Torday[1]

- Rats of the second generation exhibit increase in lung resistance after metacholine challenge
- Changes in the lung and gonad DNA methylation and histone 3 and 4 acetylation

Hypothesis of pathogenic ETS effects

Nicotine

Volatile compounds

ROS

Epigenetic modification

Epithelial type II
Cell death

Fibroblasts

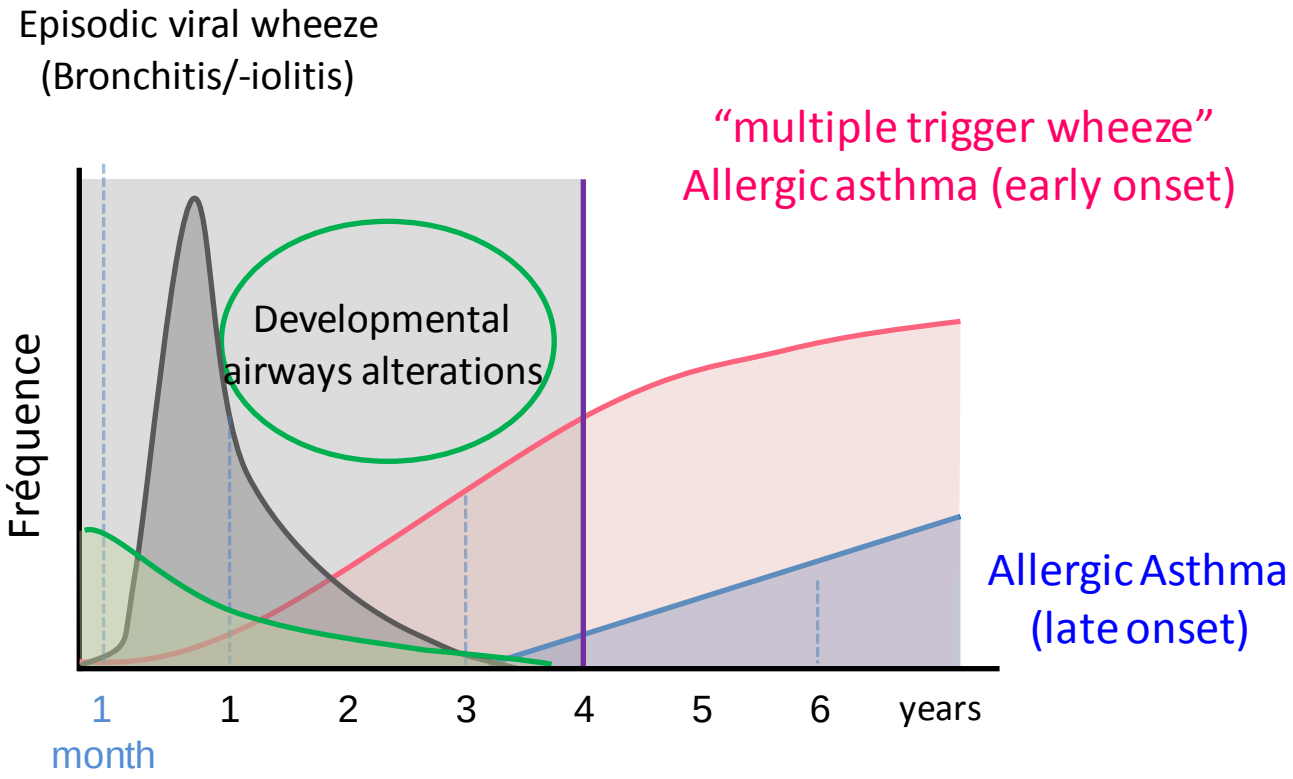
transdifferentiation

Myofibroblasts

Structure and function
alteration
of small airways

Persistance of obstructive disease
in adulthood

Advance pulmonary maturity
and lung arrest
Decrease bronchiolar formation?


Episodic viral wheeze
(Bronchitis/-iolitis)
"multiple trigger wheeze"
Allergic asthma (early onset)
Developmental
airways alterations
Fréquence
Allergic Asthma
(late onset)
1
month
1
2
3
4
5
6
years

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