

SMOKING AND HEALTH

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- Dear colleagues!
- I have checked carefully the whole presentation. Where it was necessary, I added few comments or explanatory notes. I hope, that the presentation is quite self-explanatory now. If you have any questions, please, do not hesitate to ask me any question. I will do my best to answer them as well as I can.
- My email is : krsek@med.muni.cz
- Good luck!
- Martin Krsek

WHO

- SMOKING IS THE MOST IMPORTANT SINGLE **PREVENTABLE** (!) CAUSE OF MORBIDITY AND MORTALITY
- SMOKING CONTRIBUTES TO:
 - MORTALITY: annually 6 mil. victims worldwide
 - MORBIDITY: at least to 25 different diseases
 - DISABILITY: the second leading factor

More people die every year

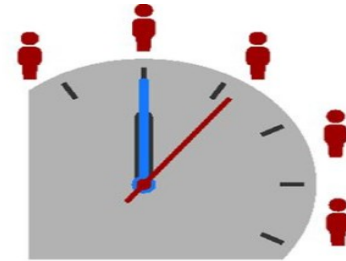
from smoking than from : murder, AIDS, suicide, drugs, car crashers and alcohol **together!**

A global pandemic



The number of people killed globally by tobacco **EVERY YEAR**

600,000 of these are killed by second-hand smoke



One person dies from tobacco every **6 SECONDS**



100 MILLION

The number of deaths from tobacco in the 20th Century



72 MILLION

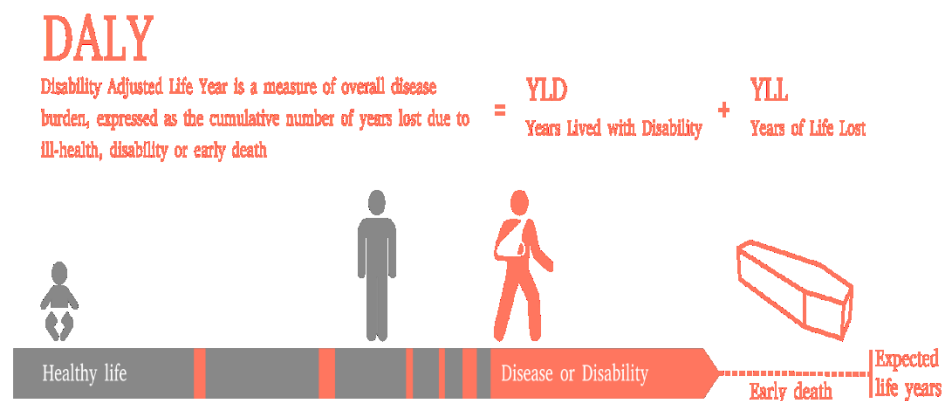
The number of deaths from war in the 20th Century (including WW1 and WW2)

GLOBAL BURDEN of DISEASES

- ATTRIBUTABLE EFFECTS of 67 **RISK FACTORS** in 21 WORLD REGIONS
- On DALYs (disability-adjusted life years) =
 - YLD (sum of years lived with disability) +
 - YLL (years of life lost)

- **FIVE LEADING FACTORS:**

- (1) HYPERTENSION
- (2) **TOBACCO SMOKING**
- (3) ALCOHOL USE
- (4) DIETARY – MALNUTRITION
- (5) PHYSICAL INACTIVITY



Smoking

- Inhalation of tobacco smoke, the most effective way for intoxication by nicotine
- Tobacco products for smoking :
 - CIGARETTES, PIPES, CIGARS
 - BIDIS, KRETEKS, STICS
 - WATER PIPES
 - SMOKELESS: SNUFF (MOIST, DRY), CHEWING TOBACCO
- NICOTINE DELIVERY SYSTEMS (e-cigarettes)
- HEATED-NOT-BURN TOBACCO PRODUCTS (IQOS –PM),
- **ALL FORMS OF TOBACCO ARE ADDICTIVE AND LETHAL**



Smoking

Nicotine content:

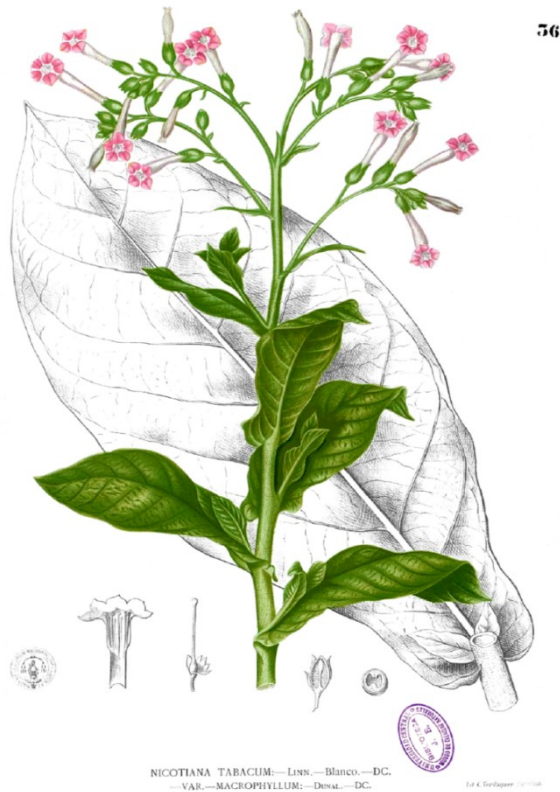
- 1 cigarette 1 - 3 mg of nicotine,
- 1 cigar cca 10 mg of nicotine

- **Inhaling**
- into mouth only - absorbs 5% of nicotine,
- deep inhalation – absorbs 70%,
- very deep inhalation with holding breath - 95% of nicotine

- human lethal dose - cca 60 mg

Tobacco plants

Nicotiana tabacum

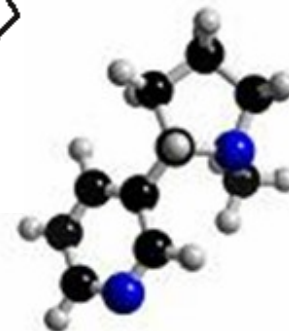
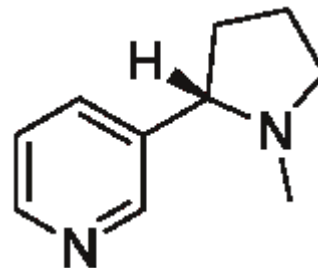


Nicotiana rustica L.



French ambassador in Portugal, Jean Nicot de Villemain sent tobacco and seeds to Paris in 1560

Nicotine



- Plant alkaloid (from plant family Solanaceae – potatoes, tomatoes, pepper,... - but no nicotine!!!)
- Human lethal dose - cca 60 mg
- Stimulating effects in nervous system
- Increase digestive tract activity, increase blood pressure, cardiac acceleration, vasoconstrictor effects, related tissue and organ hypoxia
- It is not a carcinogen itself
- **But** - its metabolites are
- E.g. NNK - nicotine-nitrosamine ketone: a strong mutagen and a carcinogen present in tobacco smoke, naturally occurring in tobacco leaves of industrially treated tobacco crops in the presence of light

IN CIGARETTE SMOKE

- ABOUT 5.000 CHEMICALS with
 - IRRITATION,
 - TOXIC,
 - CARCINOGENIC,
 - TERRATOGENIC, EMBRYOTOXIC EFFECTS

Chemicals in tobacco smoke – few examples

- **WHO: Tobacco smoke is human carcinogenic mixture**
- **arsenic** - a toxic element, used since ancient times as a rat poison
- **benzene** - carcinogenic, naturally occurring in oil, benzopyrene - a highly carcinogenic and mutagenic substance, a typical product of incomplete combustion
- **dioxins** (a group of the strongest known poisons), DDT (a very effective insecticide, until the late 1960s used to kill harmful insects, then banned in most countries) - both highly persistent
- **formaldehyde** - formerly used as an insecticide to kill moths, as a disinfectant and sterilizing agent, as a part of chipboard adhesives or in the manufacture of carpets
- **cadmium** - heavy metal, strongly cumulative in kidneys, chemically similar to Zn - blockages and changes in biochemistry. cycles (insulin cycle),
- **hydrogen cyanide** - one of the most poisonous gases (used in gas chambers during World War II, as well as a mouse poison)
- **nickel** - a highly toxic element, highly teratogenic
- **lead** - a toxic element, especially dangerous for children - causes slowing of mental development and behavioral disorders
- **TSNA** - Tobacco-specific nitrosamines - a group of highly cancer-causing substances that are **present only in tobacco products**, are involved in many types of cancer, can damage reproductive organs

Chemicals in tobacco smoke

- **Carbon monoxide** (CO) - toxic gas; preferential binding to hemoglobin molecules - decreases the amount of oxygen-transferring oxygen, significantly lower overall oxygenation of the organism. The main component of exhaust gases.
- **Nitrogen dioxide** (NO₂) - highly toxic gas, airway inflammation - from light to lung edema. They are involved in the formation of acid rains and the formation of photochemical smog.
- **Nitric oxide** (NO) - toxic gas, in the presence of corrosive moisture. In the human body it is formed in the cardiovascular and nervous system, it affects the vasodilatation, the signal molecule, the neurotransmitter function; in medicine, use in the release of smooth muscle cramps during asthma. At higher doses - heart weakness. Releases in exhaust gases and works in acid rain.
- **Tar** - A mixture of chemicals (predominantly toxic and cancer-causing) such as polycyclic aromatic hydrocarbons (PAHs) or aromatic amines; has a dense oily or greasy consistency. In tobacco smoke it is dispersed in the form of an aerosol, **90%** of which is deposited in the lungs of the smoker, 10% returns with exhaled smoke back to the atmosphere in its immediate vicinity.

SMOKING HAS

- IMMEDIATE EFFECTS
- MIDLE- TERM EFFECTS
- LONG-TERM EFFECTS

ON HUMAN HEALTH

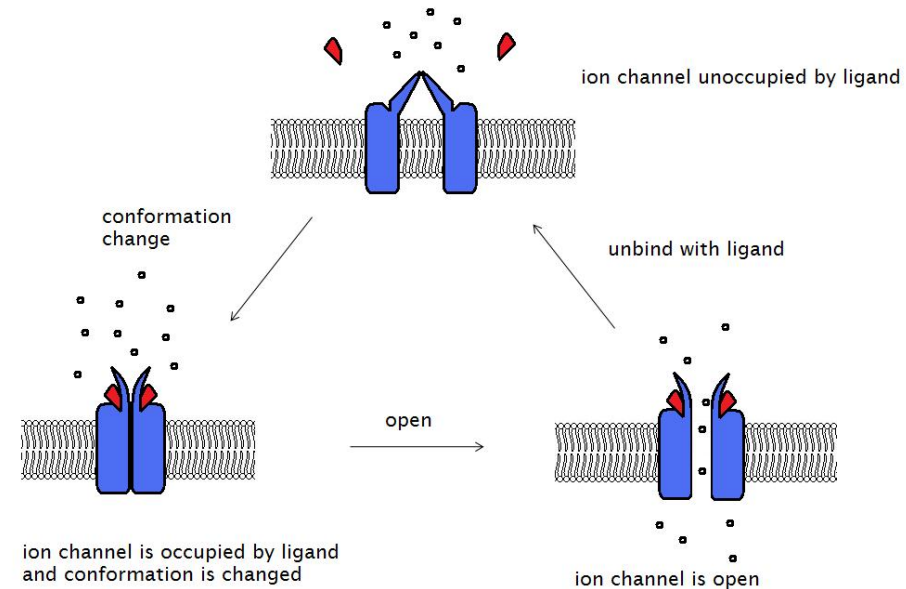
* IMMEDIATE EFFECTS

- ACTIVATION OF BRAIN RECEPTORS
- CARDIOVASCULAR CHANGES
- HYPOXEMIA
- IRRITATION

NICOTINE IN BRAIN

- NICOTINE REACHES THE BRAIN WITHIN 10-20 SECONDS AFTER THE PUFF (small molecule)
- WITHIN 20-30 MINUTES AFTER TRANSDERMAL/SALIVA TRANSPORT
- NICOTINE OCCUPIES THE SPECIFIC **CHOLINERGIC RECEPTORS** AND INDUCES THEIR ACTIVATION

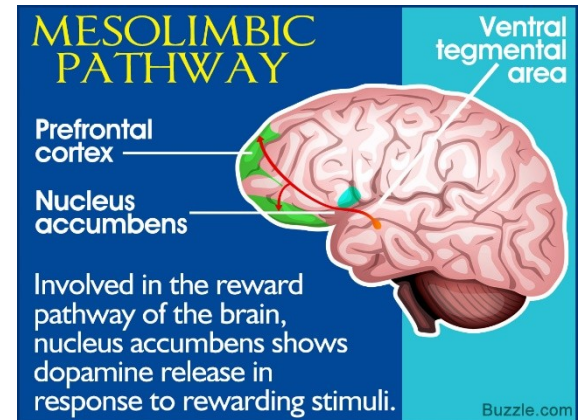
ACETYLCHOLINE RECEPTORS - nAChRs



- TWO UNITS: ALPHA, BETA
- SEVERAL SUBUNITS
- PRESENT ON NEURAL CELLS (both central and peripheral), and
- ON TISSUE CELLS
- **SOME** SUBUNITS ARE **NICOTINE SPECIFIC** (activated by nicotine)

DENSITY of nAChRs

- IN THE BRAIN IS NOT HOMOGENOUS
- ACCUMULATION IN NUCLEUS ACCUMBENS =>
- LIMBIC AREA
- AFTER THEIR ACTIVATION => SERIES OF PHYSIOLOGICAL EVENTS



RELEASE OF NEUROTRANSMITTERS:

- DOPAMINE
- SEROTONINE
- ACETYLCHOLINE
- EPINEPHRINE, NOREPINEPHRINE,
- BETA-ENDORPHINE
- ACTH (*adrenocorticotropic hormone*),
- ADRENALINE

EFFECTS OF NICOTINE

- WELL BEEING (DOPAMINE)
- COPING THE STRESS (ACTH)
- BETTER SHORT-TERM PERFORMANCE (ACETYLCHOLINE, ADRENALINE)

THESE EFFECTS

- CAN PRODUCE MANY NATURAL DAILY EVENTS:
- FOOD, SEX
- MUSIC, SUCCESS
- FRIENDLY ENVIRONMENT
- We DO NOT need nicotine for these effects!!!

DUE TO THESE REWARDS

- SMOKERS REPEATE PUFFS,
- RAISE THE NUMBER DAILY SMOKING CIGARETTES
- LIGHT ON AUTOMATICALLY IN SPECIFIC SITUATIONS
- DEVELOP ADDICTION

Two faces of tobacco companies

- NICOTINE IS THE ADDICTING AGENT IN CIGARETTES“

Private statement,
Brown & Williamson
official in 1983

„I BELIEVE THAT NICOTINE IS NOT ADDICTIVE“

Sworn testimony before
the US Congress;
CEOs of the seven leading
tobacco companies in 1994

SMOKING ADDICTION

- 80 – 85% OF CURRENT SMOKERS WILL BE DEPENDENT, SIMILARLY LIKE CURRENT USERS OF HEROINE OR COCCAINE
- ABOUT ONE THIRD OF OCCASSIONAL SMOKERS WILL BE DEPENDENT

SMOKING IS A DISEASE

- DEPENDENCE ON SMOKING IS NOT A LACK OF WILLING OR „BAD HABIT“ BUT
- CHRONICAL, PROGRESSIVE AND RELAPSING **DISEASE**
- BOTH **PHARMACOLOGICAL (nicotine)** AND **BEHAVIORAL** (the smoker lights a cigarette in certain situations – coffee, wine, friends) **ADDICTION**

Official status

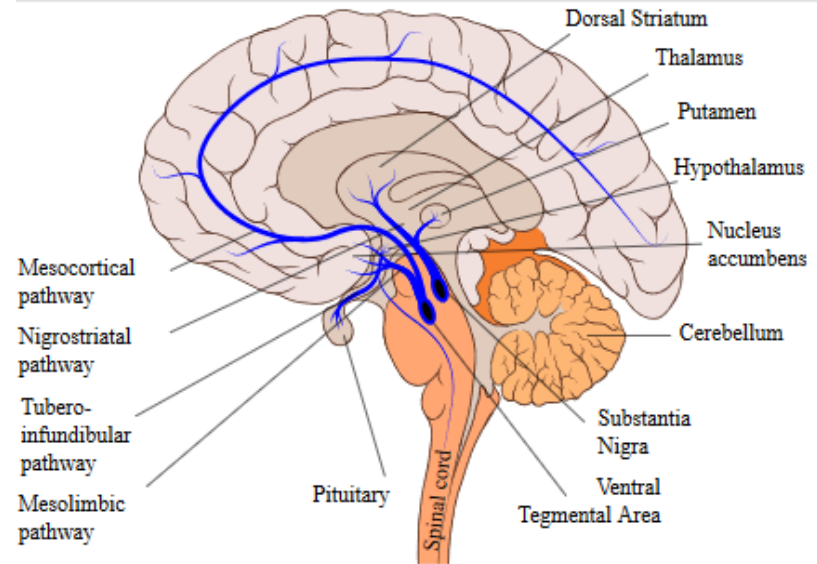
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PSYCHOLOGICAL AND BEHAVIORAL DISORDERS
CAUSED BY TOBACCO USE

International statistic classification of diseases, 10th
revision, 1991

ALTERED DOPAMINERGIC SYSTEM

- PREMATURE ACTIVATION OF **FETAL** RECEPTORS
- (30-fold higher affinity for the neurotransmitter Ach)
- DECREASED AMOUNT OF NEURAL CELLS IN THE BRAIN
- SUDDEN INFANT DEATH SYNDROME
- IMPAIRED NEURO-PSYCHOLOGICAL DEVELOPMENT
- BEHAVIORAL and COGNITIVE PROBLEMS in later life



ALTERED SEROTONERGIC SYSTEM

- MAJOR PSYCHIATRIC DISORDERS (SCHIZOPHRENIA, DEPRESSION)
- 2-3 times HIGHER FREQUENCY OF SUICIDES
- SMOKING CAUSES DEPRESSION
- DEPRESSION CAUSES SMOKING

CARDIOVASCULAR CHANGES

- VASOCONSTRICTION: SKIN, CORONARY, BRAIN, ABDOMINAL, VERTEBRAL, PLACENTAL **ARTERIES**
- HIGHER BLOOD PRESSURE
- HIGHER HEART RATE
- HIGHER HEART VOLUME/MIN
- DECREASED SKIN TEMPERATURE

MECHANISMS OF ACTION

- BY QUICK ADMINISTRATION OF NICOTINE:
- ACTIVATION OF SYMPHATETIC NERVOUS SYSTEM
- RELEASE OF SUPRARENAL HORMONES
(ADRENALINE, NORADRENALINE)

VASOCONSTRICTION

- CONTINUES EVEN AFTER THE CIGARETTE IS SMOKED
- FOR ANOTHER 30 – 45 min
- AS NICOTINE IS PRESENT IN BLOOD

HYPOXEMIA

- DECREASED AMOUNT OF BLOOD DUE TO VASOCONSTRICTION (caused by [nicotine](#))
- DECREASED AMOUNT OF OXYGEN IN BLOOD (caused by carbon monoxide – [COHb](#))
- DECREASED BLOOD-TISSUE TRANSPORT OF OXYGEN (caused by hydrogen cyanid [HCN](#))

IN PREGNANCY

- LOCAL PLACENTAL NECROSIS (caused by **cadmium**)
- POWERFULL AFFINITY OF FETAL HEMOGLOBIN TO CARBON MONOXIDE ENHANCES **COHb** LEVELS BY 25% (fetal x maternal blood)

OXIDATIVE STRESS

- **IN PLACENTAL TISSUE** IMPAIRES DEVELOPMENT AND FUNCTION DUE TO DAMAGES OF DNA,
- INCREASING : APOPTOSIS AND CELLULAR DEATH

HYPOXEMIA and HYPONUTRITION

- FETAL GROWTH RETARDATION = FETAL TOBACCO SYNDROME => programming of OBESITY, LIPID AND GLUCOSE METABOLISMS
- =>RISE RISK of CVD
- RISK OF PRE-TERM BIRTH
- RISK OF INTRAUTERINE DEATH

PRENATAL EXPOSURE

ALTERATES THE LUNG DEVELOPMENT

- MODIFIES THE REPRODUCTIVE DEVELOPMENT
- RISES THE RISK OF CONGENITAL MALFORMATIONS
- SUDDEN INFANT DEATH SYNDROME

HYPOXEMIA IN ADULTS

- HEART ATTACK (IM)
- CEREBROVASCULAR ATTACK (STROKE)
- WRINKLING, PREMATURE AGEING
- IMPAIRED WOUND HEALING
- LEG AND HAND PAIN, GANGRENE – PERIPHERAL VASCULAR DISEASE





IRRITATION

- EYES: excessive tearing, blinking, stinging
- NOSE: bad smell, stinging, phlegm
- NASOPHARYNX: cough, chest could
- STRESS DUE TO DYSCOMFORT

SHORT/MIDL-TERM EFFECTS

- IMPAIRED IMMUNITY
- HORMONAL DYSBALANCE
- IMPAIRED BLOOD LIPIDS
- IMPAIRED HEMOCOAGULATION
- CHRONIC INFLAMMATION

IMMUNE SYSTEM

- IMPAIRED RESISTANCE TO INFECTION
- CONTRIBUTION TO ALLERGIES
- INFANTS AND CHILDREN ARE THE MOST VULNERABLE POPULATION
- IMPAIRED RESISTANCE TO CANCER (Natural Killers)

MALE REPRODUCTION

- IMPOTENCE (erectile dysfunction)
- IMPAIRED SPERMIOGENESIS: deformity, loss of motility, reduced number, aneuploid sperm cells
- INFERTILITY
- FETAL MALFORMATIONS

SMOKING INCREASES ED

- FROM 2005 (Austoni et al.) studies in many populations: China, Middle East, Europe, America
- OR = 1,4 – 3.1 with respect to other causes of ED
- Smoking effects on ED are dose dependent

MOLECULAR MECHANISMS

- PARASYMPATHETIC NERVOUS SYSTEM INDUCES SMOOTH MUSCLE RELAXATION => ALLOWS ARTERIAL PRESSURE BLOOD INTO THE CORPUS CAVERNOSUM VIA ACTION of NITRIC OXIDE (NO)
- NICOTIN IS SYMPATICOMIMETIC,
- LEVELS OF NO – are altered by smoking

SMOKING CESSATION

- NO CONSISTENT RESULTS ABOUT THE MAGNITUDE OF THE BENEFITS WITH REGARD TO ED
- HISTORY OF SMOKING PRODUCE SILENT VASCULAR INSULT THAT PERSIST OVER TIME

BETTER PROGNOSIS

- IS BELIEVED FOR YOUNGER MEN WITHOUT SO LONG SMOKING HISTORY and
- WITH LACK OF COMORBIDITIES.

- Kovac JR et al. Effects of cigarette smoking on erectile dysfunction
- Andrologia 2014;
- Doi: 10.1111/and.12393

FEMALE REPRODUCTION

- PAINFUL MENSTRUATION
- EARLIER MENOPAUSE
- INFERTILITY
- ECTOPIC PREGNANCY
- PLACENTA PRAEVIA
- PREMATURE BIRTH
- SPONTANEOUS ABORTION

BOTH ACTIVE AND PASSIVE SMOKING ARE RISKS (OR):

- ACTIVE SMOKERS:

- ABORTIONS1.16
- STILLBIRTHS.....1.44
- ECTOPIC PREG. ... 1.43

PASSIVE SMOKERS

-1.17
- 1.55
- 1.61

SMOKING

- SEEMS TO BE **PROTECTIVE** for the development of PREECLAMPSIA (high blood pressure, proteins in urine)
- BUT IT IS NOT A REASON FOR KEEPING SMOKING DURING PREGNANCY!!!, AS OTHER RISKS PREVAILE THIS BENEFIT

OTHERS

- HORMONAL DYSBALANCE CONTRIBUTES TO:
- DIABETES MELLITUS and COMPLICATIONS
- OSTEOPOROSIS
- HIP FRACTURES
- By the **ANTIESTROGENIC EFFECT** OF NICOTINE

BLOOD LIPIDS

- INCREASED LEVELS OF
 - TOTAL CHOLESTEROL
 - LDL – CHOLESTEROL
 - VLDL – CHOLESTEROL

- DECREASED LEVELS OF
 - HDL- CHOLESTEROL

HEMOCOAGULATION

- ENHANCED ACTIVITY OF THROMBOCYTES and FACTOR VIII =>
- ARTERIAL THROMBOSIS (IM, stroke, gangrene in periferies)

SMOKING IS RESPONSIBLE

- FOR 25% OF ISCHEMIC HEART DISEASES
- FOR 25% OF VASCULAR DISEASES (stroke, Burger d., aneurysma, macular degeneration, cataracts)
- FOR EARLIER ATHEROSCLEROSIS
- FOR 75% OF CHRONIC OBSTRUCTIVE PULMONAL DISEASE (chr. bronchitis, emphysema)

EXPOSURE TO ETS (Environmental tobacco smoke)

- INCREASES THE RISK OF ACUTE CORONARY SYNDROME by 25 – 30 %:
- INCREASED THROMBOGENESIS and LDL-CHOLESTEROL OXIDATION
- DECREASED ABILITY TO EXERCISE
- ACTIVE INFLAMMATORY PATHWAY
- IMPAIRED VASCULAR REPAIR

SMOKING CONTRIBUTES TO

- STOMACH AND DUODENAL ULCERS
- GUM DISEASES – GINGIVITIS, PERIODONTITIS
- TEETH LOOSE
- PROGRESSION OF PRESBYACUSIS
- PSORIASIS and other skin diseases
- TREMOR

MENTAL HEALTH:

- Smoking negative influences:
 - - brain development,
 - - memory

Smoking is a **risk** factor for Alzheimer disease

Smoking is a **protective** factor for Parkinson disease

* LONG-TERM EFFECTS

- TOBACCO SMOKE CONTAINS OVER 5.000 CHEMICALS,
- 67 OF WHICH ARE CONFIRMED or SUSPECTED HUMAN CARCINOGENS (within the list of appr. 73 confirmed human chemical carcinogens)

CARCINOGENS IN SMOKE

- POLYCYCLIC AROMATIC H. (benzo/a/pyrene)
- HEAVY METALS (Cd, As)
- RADIOACTIVE POLONIUM 210
- INDUSTRIAL CARCINOGENS: beta-naphthylamine, 4-aminobiphenyle, benzene, formaldehyde

TOBACCO SPECIFIC NITROSAMINES

- formed from **nicotine** and related compounds by a **nitrosamine** reaction that occurs during the curing and processing of tobacco:
- NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
- NNAL
- NNN
- And many others

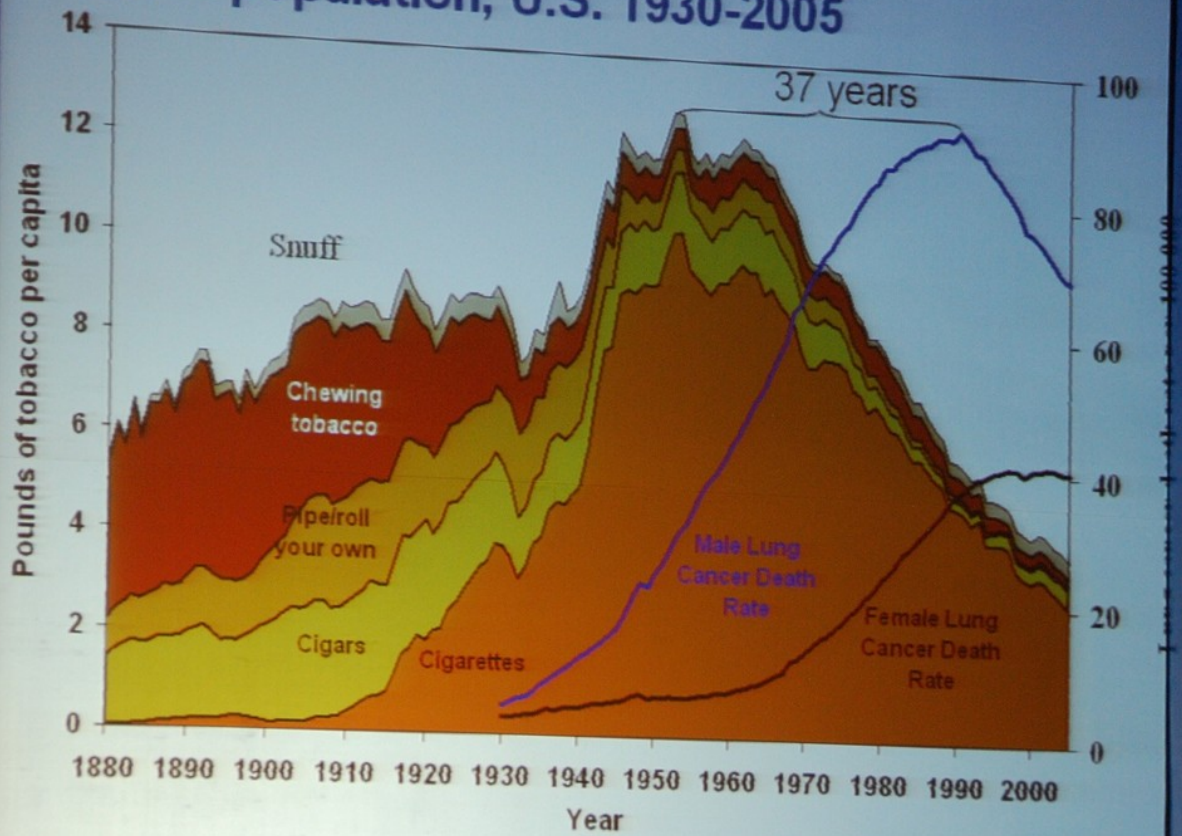
SMOKING IS RESPONSIBLE

- FOR 90-95% OF ALL LUNG CA
- FOR 40-60% OF HEAD/NECK CA
- FOR 40-60% OF KIDNEY/BLADDER CA
- FOR 30% OF CERVICAL CA
- FOR 30% OF GASTRIC/PANCREATIC CA
- FOR COLON, LIVER, BREAST CA

LUNG CARCINOGENS

- ACTIVE SMOKING 90 %
- PASSIVE SMOKING 4 %
- OCCUPATION 5 %
(radiation, asbestosis, Cr, Ni, PAH, plast additives, benzin...)
- ENVIRONMENT 1 %

Lung cancer death rates in men & women: General population, U.S. 1930-2005



PATHWAYS

- **GENOTOXICITY** => INITIATION OF CARCINOGENESIS
- METABOLIC ACTIVATION – microsomal enzymes P 450
– HEREDITARY DETERMINATION
- **EPIGENETIC EFFECTS**
 - =>MODULATE CELLULAR FUNCTIONS
 - => TUMOR PROMOTION and PROGRESSION

CARCINOGENESIS

- GENOTOXIC EFFECTS:

1. INITIATION of DNA MUTAGENIC CHANGES
2. REPLICATION

- EPIGENETIC EFFECTS:

INFLUENCE ON APOPTOSIS

1. PROMOTION
2. PROGRESSION
3. METASTASES

CONSEQUENCES: PROMOTION

- CELL'S PROLIFERATION
- ANTI – APOPTOSIS
- PROTEIN SYNTHESIS
- MITOCHONDRIA DYSFUNCTION
- INCREASING of REPLICATIVE LIFESPAN of CARCINOGENIC CELLS

CONSEQUENCES: PROGRESSION and INVASION

- ANGIOGENESIS =>
- SUPPORT FOR THE TUMOR GROWTH
- DECREASED CELLS' ADHERENCE =>
- METASTASIS

ROLE OF microRNAs

- PROBABLY MORE THAN 1000
- KNOWN MORE THAN 700
- TISSUE SPECIFIC
- DETECABLE IN 12 BODY FLUIDS
- SOME OF THEM EARLIER MARKERS OF CARCINOGENIC CHANGES

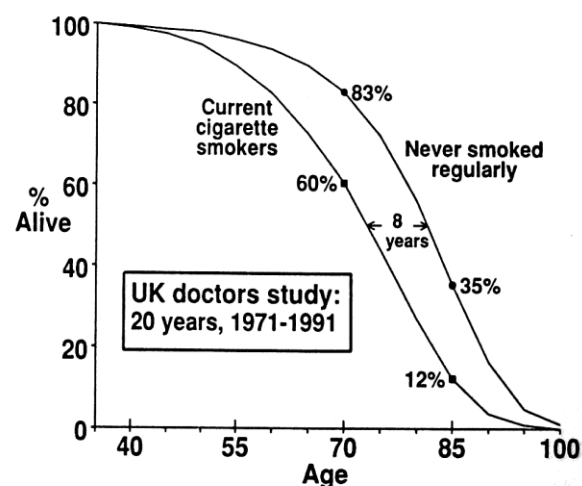
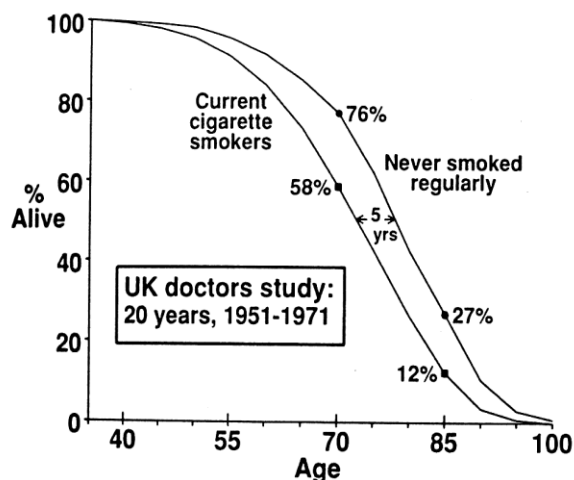
SMOKING KILLS

- HALF OF ALL LIFETIME USERS
- HALF OF THEM WILL DIE BETWEEN
30-69 YEARS OF AGE
- IN THE 20th CENTURY
100 MILLION PEOPLE DIED FROM TOBACCO USE

SMOKING KILLS PHYSICIANS

- British Medical Doctors Study (Doll, Lopez, Peto): smokers lost
- 5 YEARS OF LIFE - 1951-1971
- 8 YEARS OF LIFE – 1971-1991
- 10 YEARS OF LIFE – 1991-2006

The British Doctors' Study 1951 - 2001



The longest prospective study - addressed more than 34,000 British doctors (more than 2/3 get involved). Basic hypothesis - "Smoking is a major cause of lung cancer". In 1951-1971, the difference in life span of smokers and non-smokers was 5 years, after another 20 years 8 years, and the latest study found a 10-year loss of life for British doctors-smokers as compared to lifetime non-smokers.

SMOKING KILLS NON-SMOKERS

- MAIN STREAM (MS)
- (when smoker puffs)
 - 800-900° C
 - 16% O₂
 - 6,0-6,7 pH

- SIDE STREAM (SS)
(cigarette burning on its own)
 - 600° C
 - 2% O₂
 - 6,7-7,5 pH

DANGER FOR NON-SMOKERS

- SECONDHAND SMOKE
- ENVIRONMENTAL TOBACCO SMOKE
- PASSIVE SMOKING
- INVOLUNTARY SMOKING

Side stream + smoker's expiration + chemicals interaction

SIMILARITIES and DIFFERENCES

- THE NUMBER OF CHEMICALS in MS and SS ARE THE SAME
- THE LEVELS OF CHEMICALS ARE HIGHER in SS COMPARED TO MS
- DUE TO IMPERFEKT BURNING

RATIO SS : MS - IRRITANTS

- ACROLEIN 8 – 15
- FORMALDEHYDE 10 – 15
- AMONIUM 73
- NITROGEN OXIDES 4 – 10
- FORMAMIC ACID 1,5
- NAFTALENE 16

RATIO SS : MS - TOXINS

- CARBON MONOXIDE 2 – 5
- TOLUENE 6 – 8
- NICOTINE 2,6-3,3
- NICKEL 13 – 30
- POLONIUM 210 1 – 4
- PCDD, PCDF (dioxins, furans) 2

RATIO SS : MS - CARCINOGENS

- BENZENE 5 – 10
- NITROSAMINES 20 – 100
- 2-NAFTYLAMINE 30
- 4-AMINOBIFENYLE 30
- BENZO/A/PYRENE 2,5 – 3,5
- TAR 1,7

INDOOR CONCENTRATIONS OF NICOTINE (before the ban on smoking)

- WORK-PLACES 20 ug/m³
- CONFERENCE HALL 40 ug/m³
- RESTAURANTS 26-28 ug/m³
- CARS 40 ug/m³
- HOMES 7-11 ug/m³
- HOSPITALS 0,01- 4 ug/m³

INDOOR CONCENTRATIONS OF NITROSAMINE NNK (before the ban)

- BARS 10 – 24 $\mu\text{g}/\text{m}^3$
- RESTAURANTS 1 – 3 $\mu\text{g}/\text{m}^3$
- TRAINS 5 $\mu\text{g}/\text{m}^3$
- CARS 29 $\mu\text{g}/\text{m}^3$
- OFFICES 26 $\mu\text{g}/\text{m}^3$
- HOMES 2 $\mu\text{g}/\text{m}^3$

THIRDHAND SMOKE

- SOME CHEMICALS IN ETS ARE ABSORBED IN WALLS, CARPETS, CLOTHES, FURNITURE
- AND ARE RE-EMITTED INTO THE INTERIER

THIRDHAND SMOKE

- NICOTINE + NITRIC ACID + NO_x
- => INTERACTIONS =>
- NITROSAMINES NNK, NNA, NNN
- (mutagenic, carcinogenic)
- CONTAMINATION OF CLOTHES, SKIN, CARPETS, FURNITURE for many hours, days, weeks, years

1st EXPERIMENTAL STUDY:

- MICE EXPOSED TO **THIRDHAND SMOKE**
- **LIVER**: FIBROSIS, STEATOSIS
- **BLOOD**: INCREASED TOTAL and LDL **CHOLESTEROL**, DECREASED HDL CHOLESTEROL
- **PRE-DIABETIC** DEFECTS OF INSULIN METABOLISM
- **LUNG**: FIBROSIS, INCREASED NUMBER of MACROPHAGES => OXIDATIVE STRESS
- **SKIN**: KERATINOSIS, LESS FIBRILLAR COLLAGEN
- HYPERACTIVITY, ANXIETY

EXPOSURE TO ETS - CHILDREN

- UNPLEASANT DYSCOMFORT
- IRRITATION
- IMPAIRED IMMUNITY
- RESPIRATORY INFECTIONS, ALLERGY
- Sudden infant death syndrome
- LEUKEMIA, BRAIN TUMORS
- The most vulnerable group – immature biological structures, faster breathing frequency, lower breath zone, specific habits - climbing on four, licking hands ...

EXPOSURE TO ETS - ADULTS

- UNPLEASANT DYSCOMFORT
- IRRITATION
- ACCUTE CORONARY ISCHEMIA
- CHRONIC OBSTRUCTIVE PULMONARY DISEASE
- LUNG CANCER

HEALTH CONSEQUENCES OF EXPOSURE TO ETS:

- AN HOUR A DAY IN A ROOM WITH SMOKER IS NEARLY A HUNDRED TIME MORE LIKELY TO CAUSE LUNG CANCER IN A NON-SMOKER THAN TWENTY YEARS SPENT IN A BUILDING CONTAINING ASBESTOS

Sir Richard Doll, 1989

BAN OF SMOKING ON PUBLIC PLACES

- 18 months after implementation:
- **INCIDENCE of MI DECLINED BY 33%**
from 150.8 to 100.7 / 100.000
- **INCIDENCE of SUDDEN CARDIAC DEATH DECLINED BY 17%** from 109.1 to 92.0 / 100.000

[Minnesota Study](#) , Arch.Intern.Med. Doi: 10.1001/2013.jamainternmed.46

- Similar data in ČR

SMOKE-FREE LEGISLATION

- LOWERED RATES OF HOSPITAL ADMISSIONS for:

	RR
• CORONARY EVENTS	0.848
• OTHER HEART DIS.	0.610
• CEREBROVASCULAR DIS. ...	0.840
• RESPIRATORY DIS.	0.760

ANTENATAL EXPOSURE

- GROWTH RETARDATION
- DELAYED LUNG DEVELOPMENT
- ACTIVATION OF nAChs (by NICOTINE) = NEUROTERRATOGENICITY (CONDUCT DISORDERS, ADHD, REDUCED MENTAL / SCHOOL PERFORMANCES)

PRENATAL PROGRAMING

- EXPOSURE TO MATERNAL SMOKING
=> CHANGES IN FETAL METABOLISM
- OUTLAST AFTER DELIVERY
=> OBESITY, HYPERTENSION, DAMAGES
SERUM LIPIDS' RATES in CHILDHOOD and
ADULTHOOD

CONCLUSION

- CIGARETTE IS UNIQUE ARM KILLING BY ITS BOTH ENDS
- GLOBAL TOBACCO EPIDEMY IS WORSE TODAY THAN 50 YEARS AGO AND MAY BE WORSE IN ANOTHER 50 YEARS
- SMOKING IS THE MOST IMPORTANT PREVENTABLE RISK FACTOR

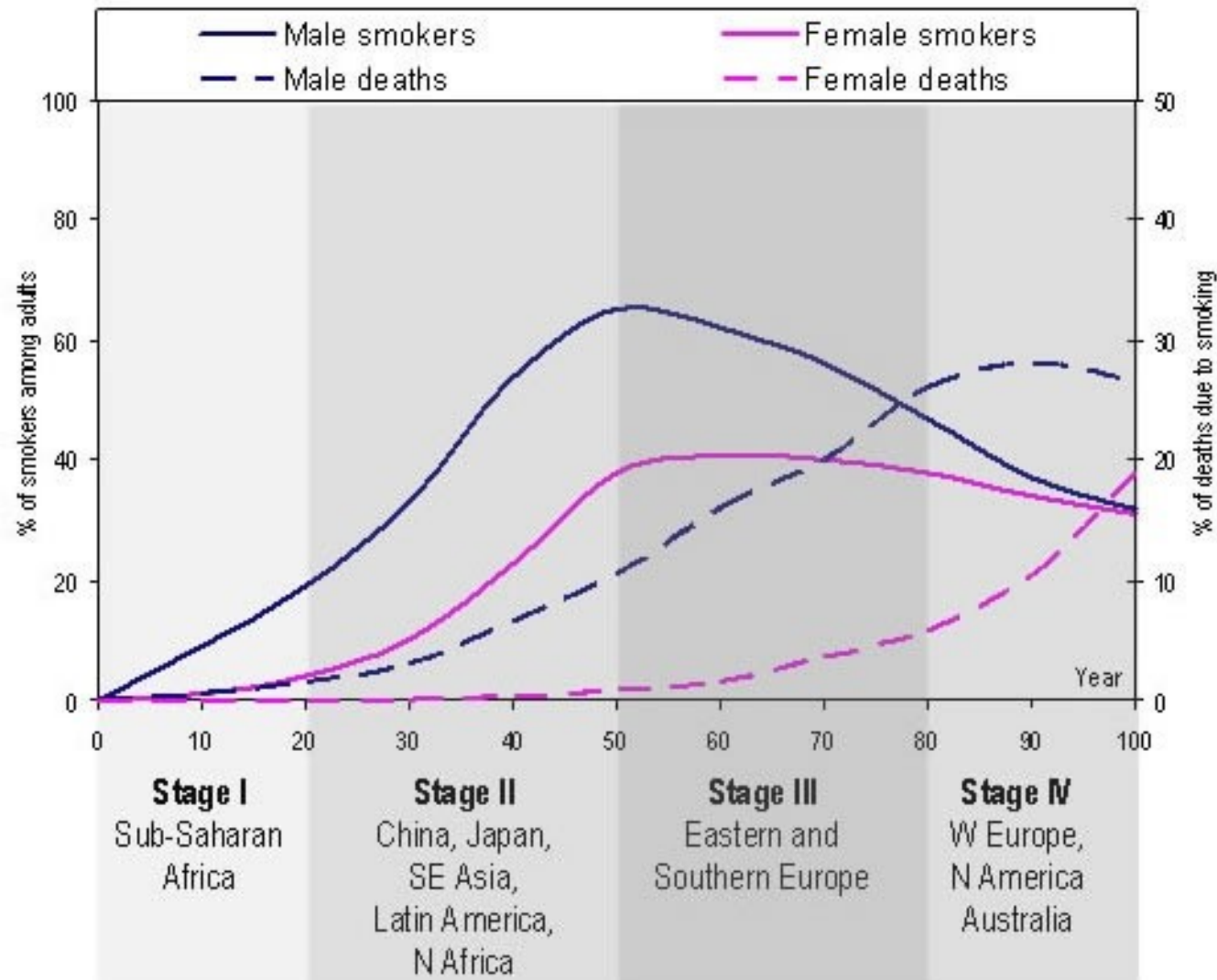
SMOKING CESSATION

DEATH *IN* OLD AGE IS INEVITABLE,
BUT DEATH *BEFORE* OLD AGE IS NOT

Sir Richard Peto, 2006

<https://is.muni.cz/www/2422/um>

Smoking epidemic/pandemic



THE RISK IS BIG

- ABOUT HALF OF SMOKERS ARE KILLED
- THOSE KILLED IN MIDDLE AGE LOSE 10, 20, 30 OR MORE GOOD YEARS

www.deathsfromsmoking.net

STOPPING SMOKING WORKS

- EVEN IN EARLY MIDDLE AGE (40y) THOSE WHO STOP, AVOID MOST OF THEIR RISK OF BEING KILLED BY TOBACCO
- STOPPING BEFORE MIDDLE AGE WORKS EVEN BETTER

Prevalence of smoking in the Czech Republic

- The overall prevalence over the past 15 years:

30% (2012) - 25.2% (2017)

By gender:

Men 36%, Women 26% (2012)

Men 30%, Women 20% (2017)

By age:

under 15 - up to 33%, 15-24 years: 43%, 25-44 years: 33%, 45-64 years: 28%, over 65: 20% (2012)

15-24 years: 36%, 25-44 years: 27%, 45-64 years: 26%, over 65 years: 15% (2017)

Prevalence of smoking in the Czech Republic

- The use of other tobacco products than cigarettes:
 - pipes, cigars, water pipes
2 - 2.5% (2012) 4.7% (2017)
 - e-cigarettes 1.7% (2012), 5.2% (2017)
 - Smokeless tobacco: 2.5% (2017)

IMMEDIATE BENEFITS OF STOPPING

- **WITHIN 20 - 30 MINUTES:**
- THE BLOOD PRESSURE AND HEART RATE WILL DROP TO THE REST VALUES
- THE SKIN TEMPERATURE (LEGS) RAISES BY 2° C

SHORT-TERM BENEFITS OF STOPPING

- **WITHIN 6 – 8 HOURS**
- COHb LEVELS WILL DROP TO THE NORMAL VALUES (< 1%)
- **WITHIN 72 HOURS**
- PULMONARY FUNCTIONS WILL IMPROVE (1sec forced expiration)

MIDDLE-TERM BENEFITS OF STOPPING

- **WITHIN 2 MONTHS**
- MALE SPERM DAMAGES CAUSED BY SMOKING WILL BE REPAIRED

- **WITHIN THE 1st TRIMESTER**
- THE RISK OF PREGNANCY PROBLEMS AND FETAL BODY POOR DEVELOPMENT WILL DECREASE

MIDDLE-TERM BENEFITS OF STOPPING

- **WITHIN 1st YEAR**
- THE BLOOD LIPID PROFILE WILL BE IMPROVED,
- THE PARAMETERS OF HEMO-COAGULATION WILL BE IMPROVED
- THE RISK OF AC. CARDIAC ISCHEMY and STROKE WILL DECREASE

LONG-TERM BENEFITS

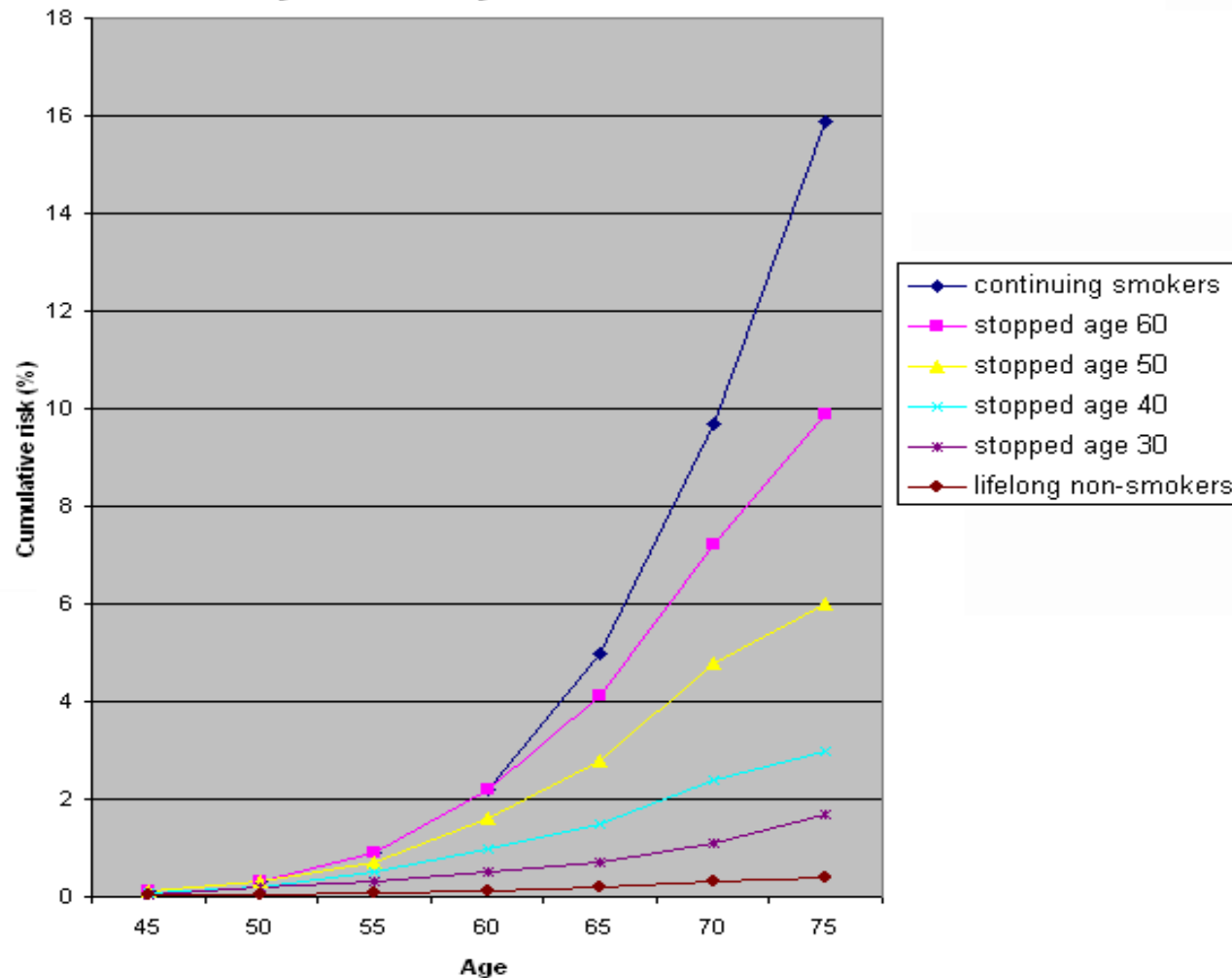
- **WITHIN 5 YEARS**
- THE RISK OF CVD DEATH WILL BE SIMILAR AS FOR NEVER-SMOKERS
- THE RISK OF SMOKING-RELATED CANCERS WILL START THE DECREASED TRENDS

LONG-TERM BENEFITS

- **WITHIN 10 – 20 YEARS**
- THE RISKS OF SMOKING-RELATED CANCER'S DEATH WILL BE SUBSTANTIALLY DECREASED, ALMOST TO THE LEVELS FOR PEOPLE WHO NEVER SMOKED

LONG-TERM BENEFITS

Figure 3. Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer by age 75, calculated by combining results from the 1990 study with mortality rates for men in the UK in 1990



CONCLUSIONS

- THE RISK IS BIG
- STOPPING SMOKING WORKS
- EFFECTIVE SUPPORT OF SMOKING CESSATION WILL CHANGE THE DEATH EPIDEMIC WITHIN 10-20 YEARS

SMOKERS ARE:

- AT THE BEGINNING:
- CURIOSITY SEEKING PEOPLE.
- UNHAPPY, UNSUCCESSFUL PEOPLE
- LAZY PEOPLE

- LATER ON:
- DEPENDENT PEOPLE

CRITERIA OF ADDICTION

- USING THE DRUG LONGER THAN EXPECTED
- USING THE DRUG DESPITE OF HEALTH PROBLEMS
- A LOT OF TIME PER DAY IS SPENT BY EFFORT TO OBTAIN THE DRUG /or BY USING THE DRUG

CRITERIA - continue

- USER NEGLECTS SOME ACTIVITIES WHERE USING OF DRUG IS BANNED
- SHORT-TERM ABSTINENCE RESULTS IN THE REPEATEDLY OCCURRING WITHDRAWAL SYMPTOMS and RELAPSE

TOLERABILITY

- THE SAME DOSE CAUSES LOWER EFFECTS
- FOR THE SAME EFFECTS THE INCREASED DOSE IS NECESSARY

WITHDRAWAL SYMPTOMS (WS)

- EXCITABILITY, NERVOUS, STRESSED
- ATTENTION DISABILITY
- COGNITIVE PROBLEMS
- DEPRESSION
- ANXIETY

WITHDRAWAL SYMPTOMS

- POORER WEIGHT CONTROL -> OVERWEIGHT
- EXPECTORATION
- CONSTIPATION

WS – TIMING

- WITHIN 2 HOURS AFTER THE LAST CIGARETTE
- WAVES WITH DIFFERENT FREQUENCY AND INTENSITY
- SEVERAL DAYS – WEEKS – MONTHS - YEARS

WS - CAUSES

- LACK OF NICOTINE
- LACK OF SOCIAL CONTACTS
- CRAVING FOR SMOKING
- INCREASED FOOD INTAKE
- DECREASED BASAL METABOLISM

WITHDRAWAL SYMPTOMS

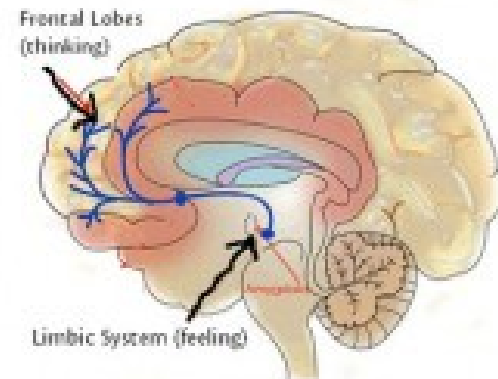
- ARE NOT HARMFUL FOR HEALTH
- ARE THE MANIFESTATION OF THE DRUG ELIMINATION
- ARE THE MOST FREQUENT CAUSE OF RELAPS

POWER OF DEPENDENCE

- IS SIMILAR AS FOR HEROINE or COCAINE: 80-85 % of current users,
- 32 % of occas.smokers, 20 % of occasional users of cocaine/heroine
- ADOLESCENTS ARE MORE VULNERABLE (the pleasure effects of smoking are perceived after lower levels of nicotine)

ADDICTION TO SMOKING

- IS A **PEDIATRIC** PROBLEM
- SMOKERS USUALLY START SMOKE BEFORE the age 18 YEARS
- TIME DISCREPANCY OF LIMBIC and FRONTAL CORTEX MATURATION =>
- DISPOSITION TO RISK and LOW RESPONSIBILITY



WHAT TO DO?

- KEEPING SMOKERS' RIGHTS:
 - TO BE INFORMED ABOUT HAZARD
 - TO BE EXCLUDED FROM RISK SITUATIONS
 - TO BE MOTIVATED TO DECISION
 - TO BE SUPPORTED IN THEIR EFFORT TO STOP SMOKING

WHAT IS THE BEST WAY?

- THE „5A“ PROGRAMME:
 1. ASK
 2. ADVICE
 3. ASSESS
 4. ASSIST
 5. ARRANGE FOLLOW-UP

http://apps.who.int/iris/bitstream/handle/10665/112836/9789241506946_eng.pdf;jsessionid=9CF5056D2A25D72B74145B5B7B1B49F2?sequence=1

1. ASK EVERY PATIENT:

- DO YOU SMOKE?
- HOW MANY CIGARETTES DAILY?
- HOW MANY YEARS?
- AT WHICH AGE DID YOU START?
- AT WHICH MORNING TIME DO YOU LIGHT YOUR FIRST CIGARETTE?
- WOULD YOU LIKE TO STOP?
- HAVE YOU SOME EXPERIENCES WITH STOPPING?

1A: CONGRATULATION

- TO EVERYBODY WHO:
- HAS NEVER SMOKE
- HAS STOPPED SMOKING:
 - ASK HIM/HER ABOUT PROBLEMS,
 - SUPPORT HIS/HER EFFORT TO BE NON-SMOKER

2. ADVICE

- TO EVERY SMOKER TO STOP, because
- FAMILY HISTORY (HEREDITARY VULNERABILITY)
- SMOKER'S HEALTH HISTORY
- CURRENT HEALTH STATUS
- SOCIAL IMAGE, MODEL ROLE
- HIS/HER CHILDREN HEALTH

ADVICE IS ESSENTIAL

- PEOPLE KNOW THE SMOKING HAZARD IN GENERAL
- PEOPLE FEEL PERSONAL IMMUNITY AGAINST THE DAMAGES
- SUCH FEELINGS ARE FALSE, ERRONEOUS AND VERY DANGEROUS

SUPPORT OF ADVICE

- USE THE BOOKLETS, LEAFLETS, PICTURES, ...
- FOR TARGET POPULATION OF SMOKERS
(CHILDREN, TEENAGERS, PREGNANT WOMEN,
WORKERS, MINORS, SENIORS...)
- RECOMMEND THE SPECIAL CENTRE

MOTIVATION TO QUIT-5Rs

- **PERSONAL RELEVANCE** TO A PATIENT
- **RISK OF SMOKING** COULD BE STRESSED
- **EMPHASIZE REWARDS** (health, money)
- **ROADBLOCKS** (identify barriers)
- **REPETITION** EACH TIME OF VISIT

3. ASSESS THE LEVEL OF DEPENDENCE

- **FAGERSTROM'S QUESTIONNAIRE:**
 - 6 QUESTIONS
 - MAXIMUM 10 „BAD POINTS“
 - 4 LEVELS OF DEPENDENCE
-
- **LOSS OF AUTONOMY**

THINKING ABOUT TREATMENT

FAGERSTROM'S QUESTIONNAIRE

- 1. How soon after you wake up do you smoke your first cigarette?
 - After 60 minutes 0
 - 31-60 minutes 1
 - 6-30 minutes 2
 - Within 5 minutes 3
- 2. Do you find it difficult to refrain from smoking in places where it is forbidden?
 - No 0
 - Yes 1
- 3. Which cigarette would you hate most to give up?
 - The first in the morning 1
 - Any other 0
- 4. How many cigarettes per day do you smoke?
 - 10 or less 0
 - 11-20 1
 - 21-30 2
 - 31 or more 3
- 5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?
 - No 0
 - Yes 1
- 6. Do you smoke even if you are so ill that you are in bed most of the day?
 - No 0
 - Yes 1

FAGERSTROM'S QUESTIONNAIRE

- **Under 3**
 - Your level of nicotine dependence is still low. You should act now before your level of dependence increases.
- **4-5**
 - Your level of nicotine dependence is moderate. If you don't quit soon, your level of dependence on nicotine will increase until you may be seriously addicted. Act now to end your dependence on nicotine.
- **6-10**
 - Your level of dependence is high. You aren't in control of your smoking— it is in control of you! When you make the decision to quit, you may want to talk with your doctor about nicotine replacement therapy or other medications to help you break your addiction.

**AUTOS (Autonomy over Smoking Checklist) (adolescents & adults)**

- Di Franza J, Wellman RJ, Ursprung S. Society for Research on Nicotine and Tobacco (SRNT) Paper 11-5. 2008

	Withdrawal Symptoms (put a ü in the column that best describes me)	Not at all =0	A little =1	Pretty well = 2	Very well = 3
1	When I go too long without a cigarette I get impatient				
2	When I go too long without a cigarette I get strong urges that are hard to get rid of				
3	When I go too long without a cigarette I lose my temper more easily				
4	When I go too long without a cigarette I get nervous or anxious				
	Psychological Dependence	Not at all =0	A little =1	Pretty well = 2	Very well = 3
5	I rely on smoking to focus my attention				
6	I rely on smoking to take my mind off being bored				
7	I rely on smoking to deal with stress				
8	I would go crazy if I couldn't smoke				
	Cue-Induced Craving	Not at all =0	A little =1	Pretty well = 2	Very well = 3
9	When I feel stressed I want a cigarette				
10	When I see other people smoking I want a cigarette				
11	When I smell cigarette smoke I want a cigarette				
12	After eating I want a cigarette				
All	Total of endorsements (1 to 12)	Don't count ticks in this column.	Count the number of ticks in the above three columns = AUTOS endorsements (Range 1-12) Sum of symptom intensity scores (max 36) divided by AUTOS endorsements = Average symptom intensity (Minimum =0. Maximum =3).		

The Hooked on Nicotine Checklist

	NO	YES
1. Have you ever tried to quit, but couldn't?		
2. Do you smoke <u>now</u> because it is really hard to quit?		
3. Have you ever felt like you were addicted to tobacco?		
4. Do you ever have strong cravings to smoke?		
5. Have you ever felt like you really needed a cigarette?		
6. Is it hard to keep from smoking in places where you are not supposed to?		
When you haven't used tobacco for a while ... OR When you tried to stop smoking ...		
7. did you find it hard to concentrate because you couldn't smoke?		
8. did you feel more irritable because you couldn't smoke?		
9. did you feel a strong need or urge to smoke?		
10. did you feel nervous, restless or anxious because you couldn't smoke?		

Reference: DiFranza JR, Savageau JA, Fletcher K, Ockene JK, Rigotti NA, McNeill AD, Coleman M, Wood C. Measuring the loss of autonomy over nicotine use in adolescents: The Development and Assessment of Nicotine Dependence in Youths (DANDY) Study. *Archives of Pediatric Adolescent Medicine.* 2002;156:397-403. <http://fmchapps.umassmed.edu/honc>.

4. ASSIST WITH THE START

- HELP TO CHOOSE THE STRONGEST MOTIVE
- INICIATE TO CHOOSE THE DAY „D“
- EVALUATE THE RISK SITUATIONS: „TO KILL TIME“, „PLEASURE“, „STRESS“

ASSIST - continue

- CHOOSE THE REPLACEMENT IN THE RISK SITUATIONS: WHAT TO DO WITHOUT CIGARETTE?
- THE DIFFICULT AVAILABILITY
- CHANGE THE ATTITUDES: CIGARETTE IS NOT A FRIEND, BUT THE WORST ENEMY

MEDICAL SUPPORT - NRT

- REPLACING NICOTIN FROM SMOKING BY OTHER SOURCES:
- CHEWING GUMS:
 - NICORETTE – 2, 4 mg: RULES FOR RIGHT CHEWING
- PATCHES:
 - NICORETTE – 16 hours – 5, 10, 15 mg
 - NIQUITINE – 24 hours – 7, 14, 21 mg



NRT - continue

- INHALERS
- SUBLINGUAL TABLETS
- ORAL/NASAL SPREY



HOW TO USE NRT?

- „AD LIBIDUM“ at the beginning (1 – 3 months)
- GRADUALLY LOWERING THE DOSAGE (next 3 months; each new lower dosage kept for 1 week, at least)

E-CIGARETTES / ENDS

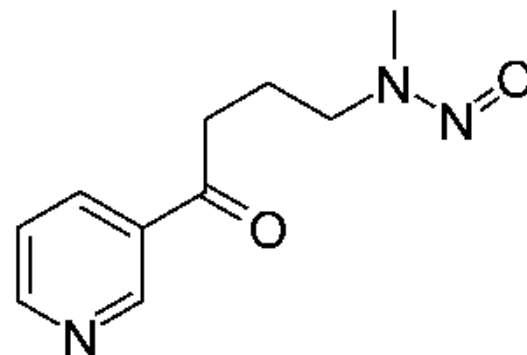
- POOR CONTROL OF INHALED NICOTINE
- OTHER HARMFUL CHEMICALS, EVEN IN LOWER LEVELS THAN IN TRADITIONAL CIGARETTES
- KEEPING THE SMOKING BEHAVIOR RITUALS
- NO KNOWLEDGE ABOUT THE HEALTH RISKS

NRT'S SAFETY AND HAZARD

- DECREASED WITHDRAWAL SY.
- SLOW RELEASE OF NICOTINE WITHOUT VASOCONSTRICTION
- CROSS PLACENTAL BARRIERE
- ANTENATAL ACTIVATION nAChRs -> NEUROTERRATOGENIC EFFECTS
- MULTIPLE CARCINOGENICITY

NICOTIN IS A COMPLETE CARCINOGEN

- NICOTIN IS NOT MUTAGENIC!
- IT CAN BE PARTIALLY METABOLISED TO NNK => INDIRECT INITIATOR OF CARCINOGENICITY
- REVASCULARISATION OF CARCINOMA/METASTATIC TISSUES => HIGHER PROGRESSION (epigenetic carcinogen)



BUPROPION

- ANTIDEPRESSIVE DRUGS:
ZYBAN, WELLBUTRINE
- COMBINATION WITH NRT

VARENICLINE - CHAMPIX

- AGONIST OF NICOTINE:
- ACTIVATION of nAChRs
- - > RELEASE OF DOPAMINE - >
- - > CIGARETTE IS NOT ONLY UNIQUE SOURCE OF PLEASURE
- ONE WEEK BEFORE STOPPING

CONTRAINDICATIONS

- IN PREGNANCY – CATEGORY C (all the supportive drugs) neuroteratogenic effect is possible (latest studies - no?)
- CHILDREN, ADOLESCENTS – NO EXPERIENCES YET (with bupropion, vareniclin)

NEW RECOMMENDATION

- TO EXCLUDE PERSONS WITH PSYCHIATRIC DISORDERS
- NEUROPSYCHOLOGICAL OBSERVATION OF VARENICLINE USERS
- CARDIOVASCULAR EVENTS

VACCINATION

- AFTER UNSUCCESSFUL ATTEMPTS: THE HIGH-MOLECULAR COMPLEX
- NICOTINE + ANTIBODIES = >
- IMPOSSIBILITY TO REACH THE BRAIN

FIRST RESULTS:

- BIVALENT VACCINE
- 5 DOSES of 400 ug
- IN ONE MONTH INTERVALS

- SAFE, SPECIFIC, RARE SIDE EFFECTS
- HIGH INDIVIDUAL VARIABILITY IN PRODUCTION OF ANTIBODIES

Duration and success of cessation

- Treatment of min. 6 months
Abstinence longer than a year - 2 - 3% of smokers can abstain alone and without help
- With counseling (treatment under professional supervision) + psychotherapy = increased success rate up to 30%
- 75 - 85% of smokers would like to stop
30-35% are trying to (repeatedly)
5 - 10% of smokers will succeed

FUTURE RESEARCH

- OPTIMAL TIME-SCHEDULE
- OPTIMAL DOSES with the respect to GENETIC POLYMORPHISM of CYP2A6
- QUICK RELEASE OF NICOTIN
- COMBINATION
- NEW TREATMENT
- NEW (safe sources of) ADDICTION

RELAPS

- TO TRY „ONLY ONE“ PUFF
- COFEE, VINE
- FRIENDS
- SEEK THE MORE PLEASURE
- STRESS
- EASY AVAILABILITY OF TOBACCO

5. ARRANGE FOLLOW-UP

- RELAPS MAY BE STRESSFUL FOR SMOKER
- TO ENHANCE SMOKER'S RECENT MOTIVATION TO STOP OR FIND NEW ONE
- BETTER ARRANGEMENT

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CONCLUSION

- THE RISK IS BIG
- STOPPING SMOKING WORKS
- THE EARLIER START OF STOPPING, =>
- THE BETTER RESULTS
- FOR SMOKER
- FOR SMOKER'S RELATIVES
- FOR THE WHOLE SOCIETY
- NOT FOR THE TOBACCO COMPANIES

April 28, 1983

Mr. Bob Kovoloff
ASSOCIATED FILM PROMOTION
10100 Santa Monica Blvd.
Los Angeles, CA 90067

Dear Bob:

As discussed, I guarantee that I will use Brown & Williamson tobacco products in no less than five feature films.

It is my understanding that Brown & Williamson will pay a fee of \$500,000.00.

Hoping to hear from you soon;

Sincerely,

Sylvester Stallone

SS/sp

The block contains two handwritten signatures. The signature on the left is 'Sylvester Stallone' written in a cursive, stylized script. The signature on the right is another name, possibly 'Williamson', also written in a cursive script. Both signatures are written in black ink and are positioned over the typed name 'Sylvester Stallone' and the typed name 'Brown & Williamson' respectively.



Self mutilation by smoking – this patient had all four limbs amputated for a Buerger's type of arteritis. His cigarette holder was made out of a coat hanger by one of his friends on the ward.

RECOMMENDATION

- FOR NO - SMOKERS:
- DO NOT START TO SMOKE
- DO NOT ALLOW TO BE A VICTIM OF RUTHLESS SMOKERS

MY RECOMMENDATION

- FOR SMOKERS:
- DO RESPECT THE NO-SMOKERS' RIGHTS TO BREATHE THE CLEAN AIR !!!
- DO CLEAN THE TOXIC WASTAGE (butts)

- DO MAKE THE RIGHT DECISION (TO STOP SMOKE)
- DO KEEP IT

BECAUSE ...

- THE LIFE WITHOUT TOBACCO IS
- MORE FREE
- MORE MODERN
- MORE CLEAN
- MORE AROMATIC
- MORE SENSUOUS
- MORE