Cigarette Smoking and Vascular Disease
Disclosure

- No relevant disclosures
Overview

- Background
- Legal Theory
- Smoking and Atherosclerosis
- Pharmacology of Nicotine
- Medical Responsibility
- References
Smoking and Global Warming
The History of Smoking

- Recorded history dates back to 5,000 BC
  - Used by shamans and priests for religious ceremonies

- Tobacco farming commercialized by John Rolfe in 1612
  - Became chief export of Virginia colony within 7 years and helped protect colonies from early French invasion
  - Promoted indentured servitude to manage the crops
  - Eventually contributed to Bacon’s Rebellion in 1676 (Nathaniel Bacon)
  - This lead to hardening of division among racial lines and eventually promoted slavery
Cigarettes

Per Capita Cigarette Consumption

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When was the first landmark case in the United States hinting that cigarettes were bad for your health?

A) 1776  
B) 1897  
C) 1944  
D) 1998  
E) 2000
“...cigarettes...are...wholly noxious and deleterious to health. Their use is always harmful, never beneficial. They...are inherently bad, and bad only and [should be] widely condemned as pernicious altogether due to impairment of physical health and mental vigor....”

_Austin v State_, 101 Tenn 563, 566-567; 48 SW 305, 306; 70 Am St Rep 703; 50 LRA 478 (1898).
Legal Failure

- Law repealed in 1917
National Tobacco Settlement

- **1998**
  - After a string of billion dollar lawsuits, big tobacco elects to settle all pending and future cases with 46 states
  - Cigarette makers agree to a $206 billion settlement known as the Tobacco Master Settlement Agreement

- **2000**
  - A Florida jury awards $145 billion in punitive damages against big tobacco after internal company records demonstrated they fully understood the connection between smoking and cancer

- **2003**
  - This award is later thrown out as unconstitutional and upheld by the Florida Supreme Court

- **2004**
  - A federal $280 billion civil racketeering (RICO) charge presses forward, but later gets thrown out in 2005

- **2007**
  - Consensus outcome leads to higher regulation of tobacco advertising and removal of “harmful” ingredients
The Poisons Within

- 2-nitropropane
- Acetaldehyde
- Acrolein
- Acrylonitrile
- Ammonia
- Aromatic amines
- Arsenic
- Aza-arenes
- Benzo (a) pyrenes
- Carbon monoxide
- Carboxylic acids
- Dimethylnitrosamine
- Formaldehyde
- Hydrazine
- Hydrogen cyanide
- Insecticide residues
- Isoprenoids
- Napthalenes
- Nickel
- Nicotine
- Nitrogen oxides
- Non-volatile nitrosamines
- Phenols
- Polonium-210
- Polynuclear aromatic hydrocarbons
- Pyridine
- Urethane
- Vinyl chloride

Source: RCP Tobacco Advisory Group
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Smoking Disrupts Endothelial Cells

Endothelial injury caused by smoking is the common pathway that leads to vascular disease and eventually worsens morbidity and mortality (Pittilo et al. 2000)

- Smoking increases cell permeability
- Nitric oxide production decreases
- ICAM / VCAM and leukocyte adherence are stimulated

These changes lead to endothelial membrane disturbances and dysfunction (Woolf et al. 1993)
Endothelial cell death is enhanced through the effects of nicotine
- Nicotine stimulates PDGF and causes intimal hyperplasia, cell structure changes, and increased permeability (Hamasaki et al. 1997)

Carbon monoxide induces oxidative stress via free radicals, and increased nitric oxide
- Enhanced conversion of LDL to atheroma occurs due to free radical damage
- This stimulates accelerated plaque development and maturation
- Endothelial damage and atherogenesis is amplified by free radicals from tar breakdown

http://medicalmyths.files.wordpress.com
Smoking and Plasma Lipoproteins

- Smoking leads to derangements in the lipid profile (Craig et al. 1989)
  - Total cholesterol (3%), triglycerides (9.1%), and VLDL (10.4%) are higher
  - A drop in HDL (-5.7%) is the most significant predictor of morbidity and mortality (Campbell et al. 2008)

- Extent of smoking influences the lipid profile
  - A dose-dependent effect is seen with cigarette consumption and lipid abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Light smokers</th>
<th>Moderate smokers</th>
<th>Heavy smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
<td>Mean (SE) Z score*</td>
<td>% Difference from value in non-smokers</td>
</tr>
<tr>
<td>Total cholesterol†</td>
<td>19</td>
<td>0.115 (0.017)</td>
<td>1.8</td>
</tr>
<tr>
<td>Triglycerides†</td>
<td>11</td>
<td>0.217 (0.027)</td>
<td>10.7</td>
</tr>
<tr>
<td>Very low density lipoprotein cholestrol†</td>
<td>2</td>
<td>0.057 (0.152)</td>
<td>7.2</td>
</tr>
<tr>
<td>Low density lipoprotein cholestrol†</td>
<td>3</td>
<td>-0.038 (0.101)</td>
<td>-1.1</td>
</tr>
<tr>
<td>High density lipoprotein cholestrol†</td>
<td>16</td>
<td>-0.173 (0.014)</td>
<td>-4.6</td>
</tr>
<tr>
<td>Apolipoprotein AI†</td>
<td>3</td>
<td>-0.226 (0.029)</td>
<td>-3.7</td>
</tr>
</tbody>
</table>

*See appendix for description of calculations.
†Linear test of trend, p<0.001.
Moderate to heavy smokers (i.e. > 1 PPD) have a relative risk increase of nearly 2 fold for vascular disease (Law et al. 1997).

The effect of cigarettes on the lipid profile is a partial explanation for this increase in risk.

The significantly higher risk of MI (2 fold) and greater morbidity and mortality is also partially explained by the effects of nicotine and the effects on platelet aggregation (McGill et al. 1988, Campbell et al. 2008).
Smoking depletes platelet nitric oxide and induces platelet aggregation.

Smoking cessation regenerates platelet nitric oxide, balances oxidative stress, and reduces agonist-induced (ADP, collagen) platelet aggregation.
Smoking and Platelet Function

Time course of platelet aggregations in subjects who quit smoking (group A, open bars) and subjects who resumed smoking (group B, solid bars)

**Virchow’s Triad**

- **Hypercoagulable state:** Increased platelet aggregation and pro-inflammatory state
- **Endothelial injury:** Direct and indirect mechanisms from release of free radicals and toxins
- **Stasis:** Disruption of laminar flow and turbulence from atherogenesis

Pittilo et al. 2000
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Physiologic Effects of Nicotine

- **Sympathomimetic**
  - Increases heart rate, blood pressure, and respiration
- **Parasympathomimetic**
  - Increases smooth muscle (GI tract) activity
  - Increases HCl production in stomach

<table>
<thead>
<tr>
<th>Positive:</th>
<th>Negative:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Emesis</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Gastrointestinal Distress</td>
</tr>
<tr>
<td>Anxiolysis</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Cerebro-vasodilation</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Cognitive Enhancement</td>
<td>Respiratory Distress</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>Seizures</td>
</tr>
</tbody>
</table>


Nicotinic Acetylcholine Receptor

- Receptors are found throughout CNS and PNS

- Activation occurs by binding of acetylcholine or nicotine, leading to depolarization and cascade activation of other voltage-gated ion channels

- Direct effect is sodium influx, but can also lead to calcium influx by activating other channels

Pharmacokinetics of Nicotine

- Each cigarette delivers about 1 mg of nicotine to the smoker
- Nicotine has a biphasic dose-dependent activity
  - Low doses lead to agonist activity
  - Very high doses lead to antagonism
- Nicotine promotes severe psychoactive dependence through the mesolimbic pathway
  - Dependence is related to nicotine and the motions associated with smoking
Elimination

- Nicotine elimination is first order (dose dependent)
- Half-life is about 2 hours
- Metabolism occurs in the liver (90%), kidney, and lungs
- Interferes with drug metabolism via P-450 system
- Excreted by kidneys and lung

*Figure 2* Simulation of plasma nicotine concentrations obtained after smoking a cigarette every hour for 16 h (based on pharmacokinetic parameters).
Smoking and Nicotine

Withdrawal

- Sleep disturbances typically last about 1 week (25% affected)
- Difficulty concentrating and the urge to smoke lasts about 2 weeks (70%)
- Irritability, depression, and restlessness lasts 4 weeks (60%)
- Oral ulcers and constipation lasts over 1 month (20-40%)
- Increased appetite lasts about 3 months (70%)
- Normalization of skin temperature, elimination of tremor, and improvement in heart rate occur in most patients due to loss of nicotinic stimulation
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Smoking is Bad

- Contributes to global warming
- Promotes indentured servitude and slavery
- Causes lots of lawsuits that later get thrown out
- Killed Lucille Ball and Johnny Carson
Smoking is Very Bad

- Increased risk of cancer in most body systems
- Bronchitis, COPD, lung cancer
- Heart disease, MI, HTN, PVD
- Osteoporosis
- CVA
- GI ulcers
- Decreased sperm count, decreased sex drive, genitourinary cancers, breast cancer
- Immune suppression and pro-inflammatory state
- Lower birth weight, birth defects, SIDS, miscarriage, mental and physical retardation
“The cigarette should be conceived not as a product but as a package. The product is nicotine. Think of the cigarette pack as a storage container for a day's supply of nicotine.... Think of the cigarette as the dispenser for a dose unit of nicotine.... Smoke is beyond question the most optimised vehicle of nicotine and the cigarette the most optimised dispenser of smoke.”

Philip Morris 1972
In major court cases dealing with smoking and its harm on people, the following arguments have been raised in support of big tobacco:

- Paternalistic strictures such as proscription of smoking in public places may violate the first, fourth, and ninth amendment
- Smoking bans impinge on autonomy and deride informed consent
- Counters utilitarian principles
  - Inhibits the smoker’s desire to be happy
- *volenti non fit injuria* – “to a willing person, no injury is done”
  - “…[t]he danger, then, is to the smoker who willingly courts it”
    - Johns-Manville Sales Corporation v. International Association of Machinists et al.
volenti non fit injuria

SURGEON GENERAL’S WARNING:
Surgery May Cause Bleeding, Infection, Disability, And May Complicate Pregnancy. It Might Kill You Too.
The Onus is Ours

- There are too many competing financial and legal interests to simply settle the issue in favor of patients
  - The questions of autonomy, constitutional restrictions, and informed consent have yet to be answered

- It is our responsibility to truly educate patients and provide a high level of informed consent on par with the procedures we perform

- As physicians and surgeons, we are in a unique position to act upon the informed consent and start medical and surgical interventions
  - We are already treating the surgical aspect of disease aggressively. Why not do the same for the medical aspects?
Synergestic Medical Management

- Unify the efforts of primary care providers, urgent care centers, surgeons, nurses, and allied health professionals with regard to smoking cessation

- Pool resources into a central repository to create an educational and interventional multidisciplinary program accessible to patients and health care providers
Smoking Cessation Portal

Patient

Coordinating Mid-Level

Smoking Cessation Portal

Consultants & Specialists

Primary Care
Principles of Smoking Cessation Success

- Strong social support with family, community support group, and health care professionals
  - Weekly meetings for the first month w/ family and community
  - Monthly meetings w/ mid-level and PCP

- Education of adverse effects and available assistance (medications, community groups)

- Multidisciplinary medical interventions (patch, gum, Chantix, bupropion SR)

- Longitudinal monitoring and reinforcement program
Evaluation of Outcomes

- Monitor patient access to resources, visits to support groups, and clinic visits
  - Readily accessible by patients and health care providers, such as a protected website

- Centralize and integrate resources together to facilitate patient access to health care providers
  - i.e. schedule appointments to start Chantix or meet with mid-levels

- Monitor time free of smoking as an indicator of short-term success

- Monitor annual lipid profiles and other indicators during follow-up
www.StopSmoking.com
References
