Neurobiology of Tobacco Dependence

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What we are up against!
Cigarettes and Tobacco Dependence

- Cigarette smoke – complex mixture of 4,000 chemicals with over 60 known carcinogens
- Most efficient delivery device for nicotine that exists-better than intravenous
- Cigarette manufacturers have modified cigarettes over the past decades to maximize nicotine delivery to the brain
- High doses of arterial nicotine cause upregulation of the nicotinic acetylcholine receptors
- Genetic factors influence tobacco dependence
- Left untreated 60% of smokers die from a tobacco-caused disease

Hurt RD, Robertson CR JAMA 280:1173, 1998
Cigarette Smokers in the US

• 88% of adult smokers began before age 18
• Each day >3800 teens have their 1st cigarette and >1000 become daily smokers
• Causal relationship between tobacco company advertising and promotion and the initiation and progression of tobacco use in young people
• In 2008 cigarette companies spent $9.8 billion on advertising and promotion which is 48% higher than in 1998
• 44% of adult smokers try to stop each year but <5% achieve long-term smoking abstinence

Dynamic Sequence of Gray Matter Maturation Over the Cortical Surface

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Maturation starts at the back of the brain ... and moves to the front

- **Cerebellum**: Physical coordination, sensory processing
- **Nucleus Accumbens**: Motivation
- **Amygdala**: Emotion
- **Prefrontal Cortex**: Judgment

Notice: **Judgment** is last to develop!
• Why would anyone smoke with this hanging over their head?
• It is in the brain!
Nicotine

- Not a carcinogen
- Liquid in its native state
- Distilled from burning tobacco and carried on tar droplets
- Only free (unprotonated) nicotine crosses biological membranes
- Inhalation → peak arterial concentrations 2-4 X venous concentrations
- Half-life 120 minutes
Nicotinic Acetylcholine Receptors
Unique in Biology

- Up-regulated by high arterial doses of nicotine
- Nicotine resets sensitivity of brain reward systems to ↑’d levels
- Indelible “memory” of its effect on reward systems
- Down-regulation takes months of smoking abstinence
- This indelible “memory” evoked by external cues → craving

Kenny, PJ and Markou A, Neuropsychopharm 31:1203, 2005
Plasma Concentration after Smoking

1 Cigarette (n=1)

- Plasma Nicotine (ng/ml)
- ARTERIAL
- VENOUS

Time (minutes)

-1 0 2 4 6 8 10

50 mg Cocaine (n=6)

- Plasma Cocaine (ng/ml)
- ARTERIAL
- VENOUS

Time (minutes)

-2 0 2 4 6 8 10

CLINIC
Temporal Cortex

A. Nonsmoker

B. Smoker

Cortical Layers

I-III  IV  V  VI
Smoking Saturates Nicotinic Receptors

- Radioligand allows for visualization of $\alpha_4\beta_2$ nAChRs
- Position Emission Tomography (PET) Scans
- 11 smokers had 14 PET scan sessions
- Smoked: none, 1 puff, 3 puffs, 1 cigarette or 2-3 cigarettes (satiety)

*Brody, A.L. Arch Gen Psychiatry. 63;907-915, 2006*
Smoking Saturates Nicotinic Receptors

Brody, A.L. Arch Gen Psychiatry. 63;907-915, 2006
Effect of SHS on $\alpha_4 \beta_2$ nAChR’s

- 11 smokers and 13 nonsmokers: 1 hour SHS exposure in passenger seat of car
- Smoker smoked mean 3.7 cigarettes during the hour $\rightarrow$ C0 inside car $\geq$ 7 ppm
- Venous nicotine 0.17 ng/mL in nonsmokers and $\uparrow$ 0.21 ng/mL in smokers
- PET scans before and after SHS exposure
- 19% occupancy of $\alpha_4 \beta_2$ nAChR’s in smokers and nonsmokers
- 23% $\uparrow$ craving in smokers after SHS exposure
We believe the products we make are not injurious to health.

We accept an interest in people’s health as a basic responsibility, paramount to every other consideration in our business.

We always have and always will cooperate closely with those whose task it is to safeguard the public health.
...defend itself on three major fronts -- litigation, politics, and public opinion. -- creating doubt about the health charge without actually denying it
SMOKING AND HEALTH PROPOSAL

What we want to do this morning is to take a summary look at the smoking and health question and then make a proposal to you for a B&W project to counter the anti-cigarette forces.

To summarize the anti-cigarette activities I think we can say that:

First - They have managed to bring us from a simple conflict of attitudes to a state of condemnation and severe restriction.

Second - Their efforts have been aggressive while ours have been defensive.

Third - The anti activities are rather orderly - almost as if they had a plan working for them.

CONFIDENTIAL
Doubt is our product since it is the best means of competing with the “body of fact” that exists in the mind of the general public.
It is also the means of establishing a controversy.
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 a dispenser for a dose unit of nicotine:
What we need to know above all things is what constitutes the hold of smoking, that is, to understand addiction.
We believe that we have found possible reasons for addiction in two other phenomena that accompany steady absorption of nicotine. Experiments have so far only been carried out with rats, but with these it is found that certain rats become tolerant to repeated doses and after a while show the usual nicotine reactions but only on a very diminished scale.
There seems no doubt that the “kick” of a cigarette is due to the concentration of nicotine in the blood-stream and this is a product of the quantity of nicotine in the smoke and the speed of transfer of that nicotine from the smoke to the blood-stream.

Nicotine is in the smoke in two forms as free nicotine base (think of ammonia) and as a nicotine salt (think of ammonium chloride) and it is almost certain that the free nicotine base is absorbed faster into the blood-stream.
Forms of Nicotine vs. pH

Distribution of protonated and unprotonated nicotine in solution at various pH increments.
All evidence indicates that the relatively high smoke pH (high alkalinity) shown by Marlboro (and other Philip Morris brands) and Kool is deliberate and controlled.
Methods which may be used to increase smoke pH and/or nicotine “kick” include:...(3) use of alkaline additives, usually ammonia compounds, to the blend.
AT is the key to competing in smoke quality with PM worldwide.
FACTORS CONTRIBUTING TO GROWTH OF LIGHTS WORLDWIDE

1952  Kent KSF with Micronite filter, first U.S. KSF

1956  Kent reduces deliveries and introduces New Micronite Filter, without asbestos!

1960  Filters rise to 50% US Domestic sales from 2% in 1950 (leading brands: Pall Mall Plain, Camel Plain)

1964  - US Surgeon General’s report ‘proves’ link between smoking and cancer
      - US National roll-out of Marlboro Country campaign ("Come to where the flavor is, come to Marlboro Country")
To 1 out of every 3 cigarette smokers:

Kent — the one cigarette that can show you proof of greater health protection

Every week, millions see convincing evidence that KENT's "Micronite" Filter is the cigarette filter that really works — giving true smoking pleasure, yet removing up to 7 times more nicotine and tar than other filter cigarettes.

If you're 1 out of 3 smokers — you're sensitive to the care and quality of tobacco, you want more than just a promise that a filter-tip cigarette will give you the health protection you need.

And KENT is the one cigarette that gives you more than a promise. Every week, on television and in store displays — the effectiveness of KENT's Micronite Filter is proved before your very own eyes... smolder against other filter-tipped brands, admired at random by packages bought at retail!

The pictures shown here are actors from one of those tests — performed by Jonathan Winters, your host on the exciting TV show, The Net.

Kent

with exclusive MICRONITE Filter

full smoking pleasure... plus proof of the greatest health protection ever

1. Everything equal. Two identical glasses made with carbon through which smoke can be drawn are placed on a single sheet of paper. When smoke from Jonathan Winters' filter cigarettes is drawn into the left glass and the smoke from a Kent Filter cigarette is drawn into the right glass, the difference in the smoke is immediately apparent.

2. Millions watch him. Millions smoke from the Kent into one glass, smoke from Brand X into the other. Notice that the smoke does not meet his mouth, it is drawn into the glasses readily as it moves through the filter of the cigarette — exactly as it would enter your mouth if you were smoking.

3. Time is checked. White allows a few minutes for the smoke to pass through the filter. No. 2, white paper, is placed in the middle of the glasses. After that, Jonathan's Filter tip cigarettes, white filter tips, are placed in the glasses. After a few minutes, the glasses are switched, and the smoke is directed back through the filter tips. The glasses are switched again, and the smoke is directed through the filter tips. In the Kent glasses, the white paper shows the smoke is the same, but in the other glasses, the white paper shows the smoke is different.

4. And here's your answer. What the glasses show, you can see a Kent filter tip can remove the smoke of a Kent Filter and a filter tip of the other cigarettes, but it can't remove the smoke of a Kent Filter and a filter tip of the other cigarettes. So, the glasses show that KENT Filter tip cigarettes are the only cigarettes that you can buy.

5. Against all claims. Here are the results of the same test performed in a laboratory, showing how KENT's Micronite Filter compares with other filter tips. When the glasses are switched, the glasses show the difference between KENT and other filter tips. The glasses show that KENT Filter tip cigarettes are the only cigarettes that you can buy.
1983  PM becomes US no. 1 selling cigarette company (ahead of RJR)

1995  Marlboro Lts family passes Marlboro FF family in US Domestic

- The big companies always regarded lowered tar as helping smokers exit the market, a suicide strategy. Continuous and unrelenting pressure on the industry by Government Health Authorities has forced all players to GO LIGHTS......
“All work in this area should be directed towards providing consumer reassurance about cigarettes and the smoking habit.”

“This can be provided in different ways, e.g., by claimed low deliveries, by the perception of low deliveries and by the perception of ‘mildness.’”
“People believe that cigarettes low in tar and nicotine have different ‘tobacco’ ingredients and different kinds of filters than other cigarettes.”

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“the tobacco is milder or a special mild blend, perhaps treated to remove tar and nicotine...”

“the tobacco is milder or a special mild blend, perhaps treated to remove tar and nicotine...”

“Those who smoke low tar and nicotine cigarettes generally do so because they believe such cigarettes are ‘better for you.’”
“It appears that we have sufficient expertise available to ‘build’ a lowered mg tar cigarette which will deliver as much ‘free nicotine’ as a Marlboro, Winston or Kent without increasing the total nicotine delivery above that of a ‘Light’ product.”

“There are products already being marketed which deliver high percentage ‘free nicotine’ levels in smoke, i.e., Merit, Now.”
"The smoker profile data reported earlier indicated that Marlboro Lights cigarettes were not smoked like regular Marlboros..."
“In effect, the Marlboro 85 smokers in this study did not achieve any reduction in the smoke intake by smoking a cigarette (Marlboro Lights) normally considered lower in delivery.”
“Low Tar Low Nicotine” Cigarettes
FTC Method

- Determines relative yield of individual cigarettes by smoking them in a smoking machine
- Machine draws 35ml puff of 2 seconds duration every minute
- Cigarette smoked down to 23mm butt length
- Cambridge filter collects the particulate matter
- Does not measure the gas phase “free nicotine”
- 2008 no longer used and as of June 2010 no longer can use “light” terminology
“Low Tar Low Nicotine” Cigarettes
Ventilation

• Ventilation holes one of key technologies to manipulate tar and nicotine yields
• Electrostatic or laser perforations of the filter or paper
• Ventilation holes in most brands are not visible
• 2/3’s of U.S. smokers are unaware of ventilation holes or that blocking then increases tar/nicotine yield
• Many smokers block (consciously or not) the ventilation holes with their lips on fingers
Smokers vs. Machines

<table>
<thead>
<tr>
<th>Nicotine Yield</th>
<th>≤0.8 mg</th>
<th>0.9-1.2 mg</th>
<th>FTC Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puff volume (ml)</td>
<td>48.6</td>
<td>44.1</td>
<td>35</td>
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<tr>
<td>Puff duration (sec)</td>
<td>1.5</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Puff no.</td>
<td>12.7</td>
<td>12.1</td>
<td>8-10</td>
</tr>
</tbody>
</table>

Carcinogens Excreted by Smokers of Regular or “Light” Cigarettes

- 150 smokers of regular or “light” cigarettes
- Serum cotinine and urine NNAL, NNAL-Gluc, and 4 aminobiphenyl hemoglobin adducts.
- Essentially the same concentrations of NNAL & 4-ABP were present in “light” or regular cigarette smokers.

Bernert J.T., et. al. Nic & Tob Res 7:729, 2005
Old Brand Line

Regular Full Flavor

New Brand Line

Lights

Ultra Lights

Sample Note from online retailer:
Formerly known as Light, Pall Mall has changed the name to Blue. These are the same cigarettes.
<table>
<thead>
<tr>
<th>Old Pack</th>
<th>New Pack Identifier</th>
<th>New Pack Available In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Pack</td>
<td>Parliament (Blue Pack)</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Parliament (White Pack)</td>
<td>Box and Soft Pack</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Parliament (White Pack) 100's</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Parliament Menthol (Green Pack)</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Parliament Menthol (White Pack)</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Parliament Menthol (White Pack) 100's</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Parliament Menthol Silver Pack</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Parliament Silver Pack</td>
<td>Box</td>
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</tbody>
</table>

**Virginia Slims**

<table>
<thead>
<tr>
<th>Old Pack</th>
<th>New Pack Identifier</th>
<th>New Pack Available In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Pack</td>
<td>Virginia Slims Gold Pack</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Virginia Slims Silver Pack</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Virginia Slims Menthol</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Virginia Slims Menthol Gold Pack</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Virginia Slims Menthol Silver Pack</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Virginia Slims 120's Gold Pack</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Virginia Slims 120's Silver Pack</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Virginia Slims 120's Menthol Gold Pack</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Virginia Slims 120's Menthol Silver Pack</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Virginia Slims Superslims Gold Pack</td>
<td>Box</td>
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</table>

**L&M**

<table>
<thead>
<tr>
<th>Old Pack</th>
<th>New Pack Identifier</th>
<th>New Pack Available In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Pack</td>
<td>L&amp;M</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>L&amp;M 100's</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>L&amp;M Blue Pack</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>L&amp;M Blue Pack 100's</td>
<td>Box</td>
</tr>
</tbody>
</table>

**Basic**

<table>
<thead>
<tr>
<th>Old Pack</th>
<th>New Pack Identifier</th>
<th>New Pack Available In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Pack</td>
<td>Basic Full Flavor</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Basic Full Flavor 100's</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Basic Full Flavor 100's</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Basic Lights</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Basic Lights 100's</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Basic Menthol Lights</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Basic Menthol Lights 100's</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Basic Menthol Ultra Lights</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Basic Menthol Ultra Lights 100's</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Basic Ultra Lights</td>
<td>Box</td>
</tr>
<tr>
<td>Old Pack</td>
<td>Basic Ultra Lights 100's</td>
<td>Box</td>
</tr>
<tr>
<td>New Pack</td>
<td>Basic Ultra Lights 100's</td>
<td>Box</td>
</tr>
</tbody>
</table>

The following packings will remain unchanged:
- Virginia Slims
- Virginia Slims Superslims
- L&M Bold
- L&M Bold 100's
- L&M Menthol 100's
- Basic Menthol 100's

*Available in Box and Soft Pack

FOR TRADE USE ONLY. NOT TO BE SHOWN OR DISTRIBUTED TO CONSUMERS.
Out with the old & in with the new...

A Year Ago...

Today...
# SALEM – Manufactured by RJ Reynolds

## Old Brand Line

<table>
<thead>
<tr>
<th>Regular Full Flavor</th>
<th>Lights</th>
<th>Ultra Lights</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Old Brand Line: Regular Full Flavor" /></td>
<td><img src="image2" alt="Old Brand Line: Lights" /></td>
<td><img src="image3" alt="Old Brand Line: Ultra Lights" /></td>
</tr>
</tbody>
</table>

## New Brand Line

| ![New Brand Line: Box](image4) | ![New Brand Line: Gold Box](image5) | ![New Brand Line: Silver Box](image6) |

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Massachusetts Department of Public Health
Change in Nicotine Yields 1998-2004

MDPH testing better simulates smoker’s behavior than FTC smoking machines.

Larger puff volume, shorter interval between puffs and 50% coverage of ventilation holes.

No significant difference in total nicotine content of the 116 brands tested.


93% of cigarettes tested were “high yield” nicotine compared to 84% tested in 1998.
“In short defendants have marketed and sold their lethal product with zeal, with deception, with the single-minded focus on their financial success, and without regard for the human tragedy or social costs that success exacted.”

- United States et.al. v. Philip Morris et. al. (2006)

Honorable Gladys Kessler, United States District Court for the District of Columbia
No matter how innocent they appear, the tobacco industry **CANNOT BE TRUSTED!**