

# ***DRUGS OF ADDICTION:***

A Survey of their Pharmacology  
& Pathophysiology

Douglas L. Bovee, MD, FACP

Addiction Medicine Specialist

January 14, 2014

# ***BACKGROUND:***

## ***Douglas L. Bovee, MD***

- Pharmacy and pharmacology background
- Medical school
- Residency in Internal Medicine
- Adult primary care
- Addiction Medicine: diagnosis and treatment and referral of drug dependency, tx of complications, and education
- Active in the realm of health care systems and public health

# *Goals*

- Inform group about personally and professionally important material
- Reinforce some of the material presented in other parts of the course
- Personalize the value of the info
- Connect the material to what is happening in health care reform
- Stimulate further inquiry and/or research into addiction medicine

# Triple Aim of Health Care Transformation

- Improve patient care—esp the individual's experience of care
- Improve health outcomes—ie improve health of our community
- Reduce costs—Currently health care costs are the biggest driver of our increasing national debt

# New Definition of Addiction (1/12)

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry.

Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

# *Definition of Alcoholism*

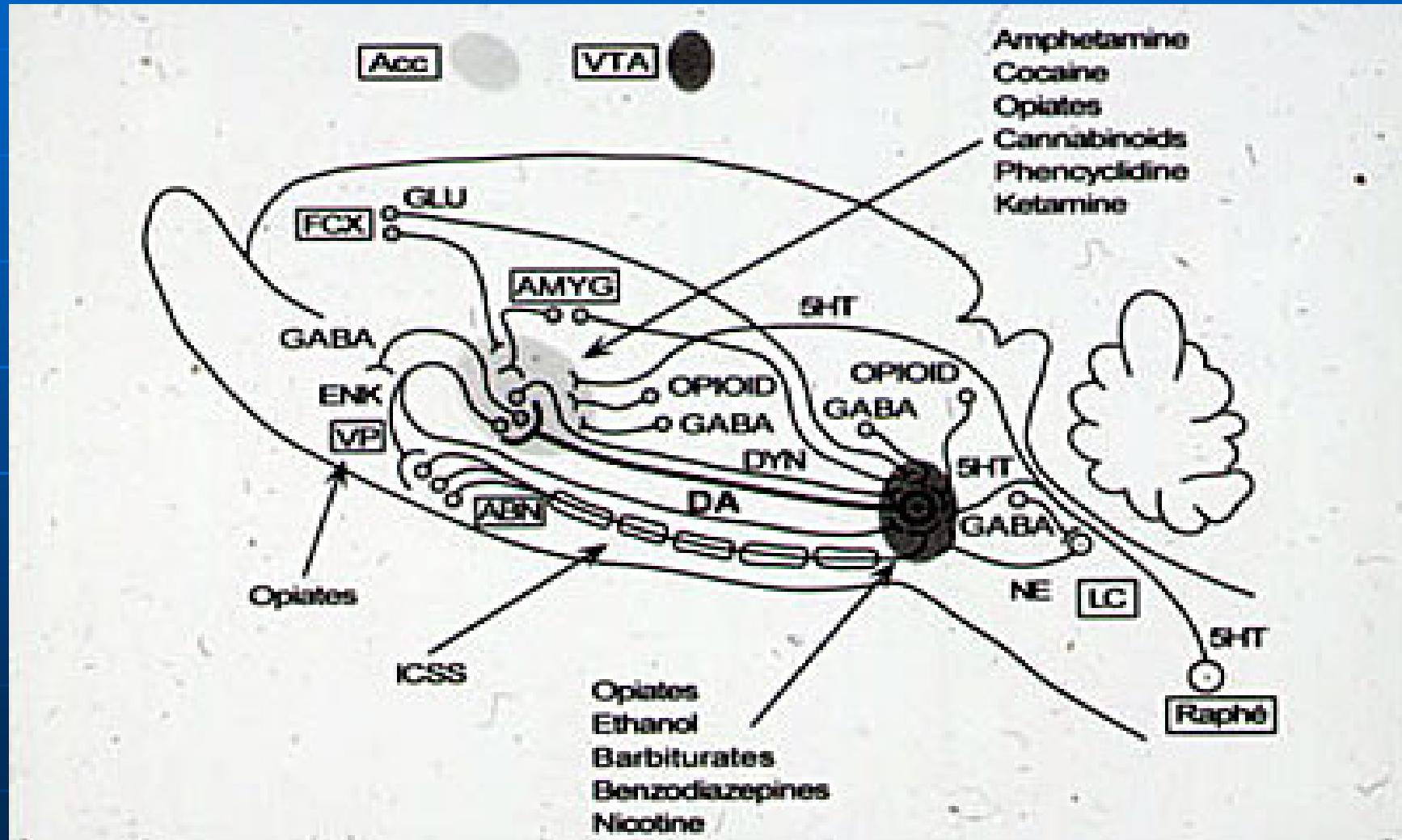
**A disease characterized by continuous or periodic:**

- Impaired control over drinking
- Preoccupation with the drug ethanol (beverage alcohol)
- Use of alcohol despite adverse consequences
- Distortions of thinking, most notably denial

# Characteristics of Addiction

- Loss of control
- Craving and compulsion
- Continued use despite adverse consequences

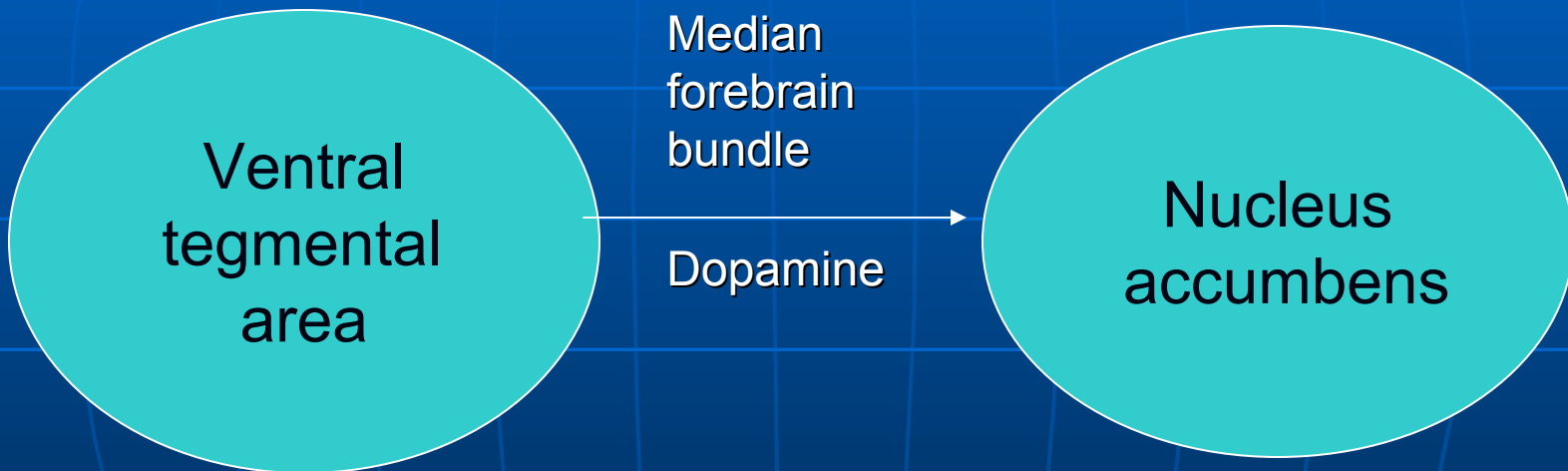
# Reward center





# Reward Pathway

This system is activated by drugs of abuse

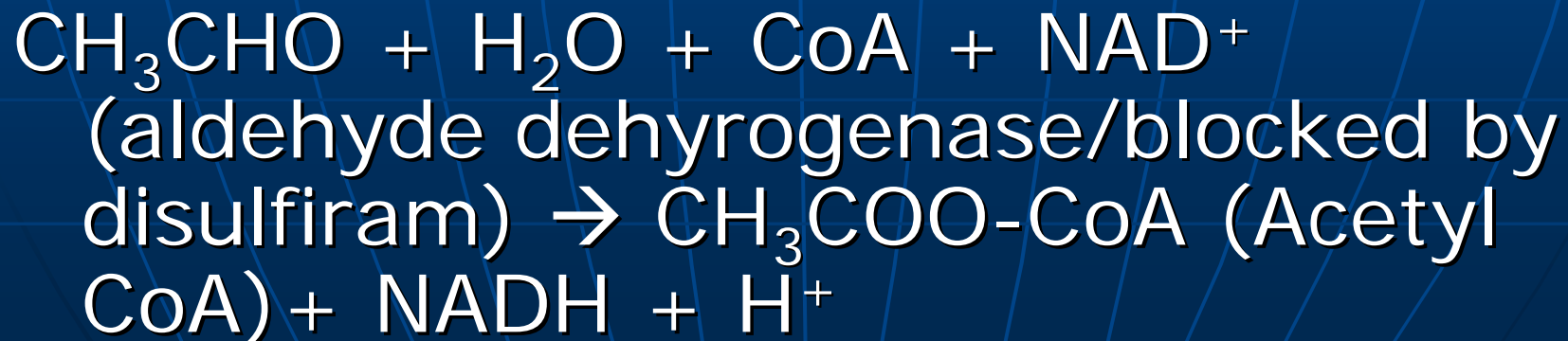
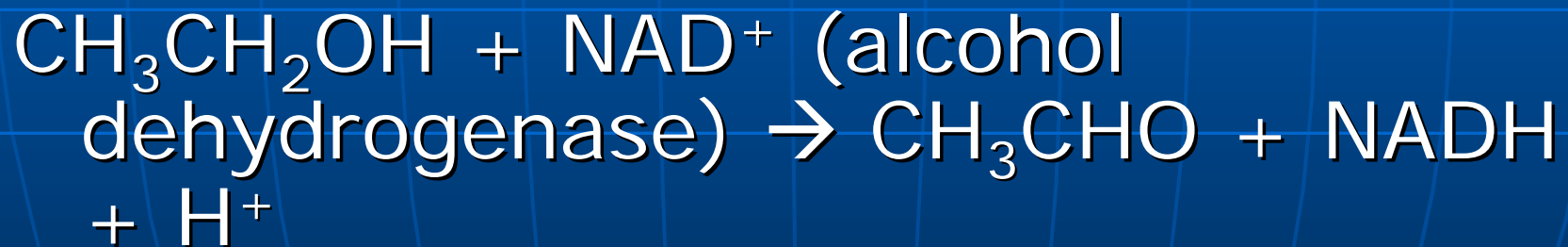


# Pharmacokinetics: the study of the movement of a drug thru the body

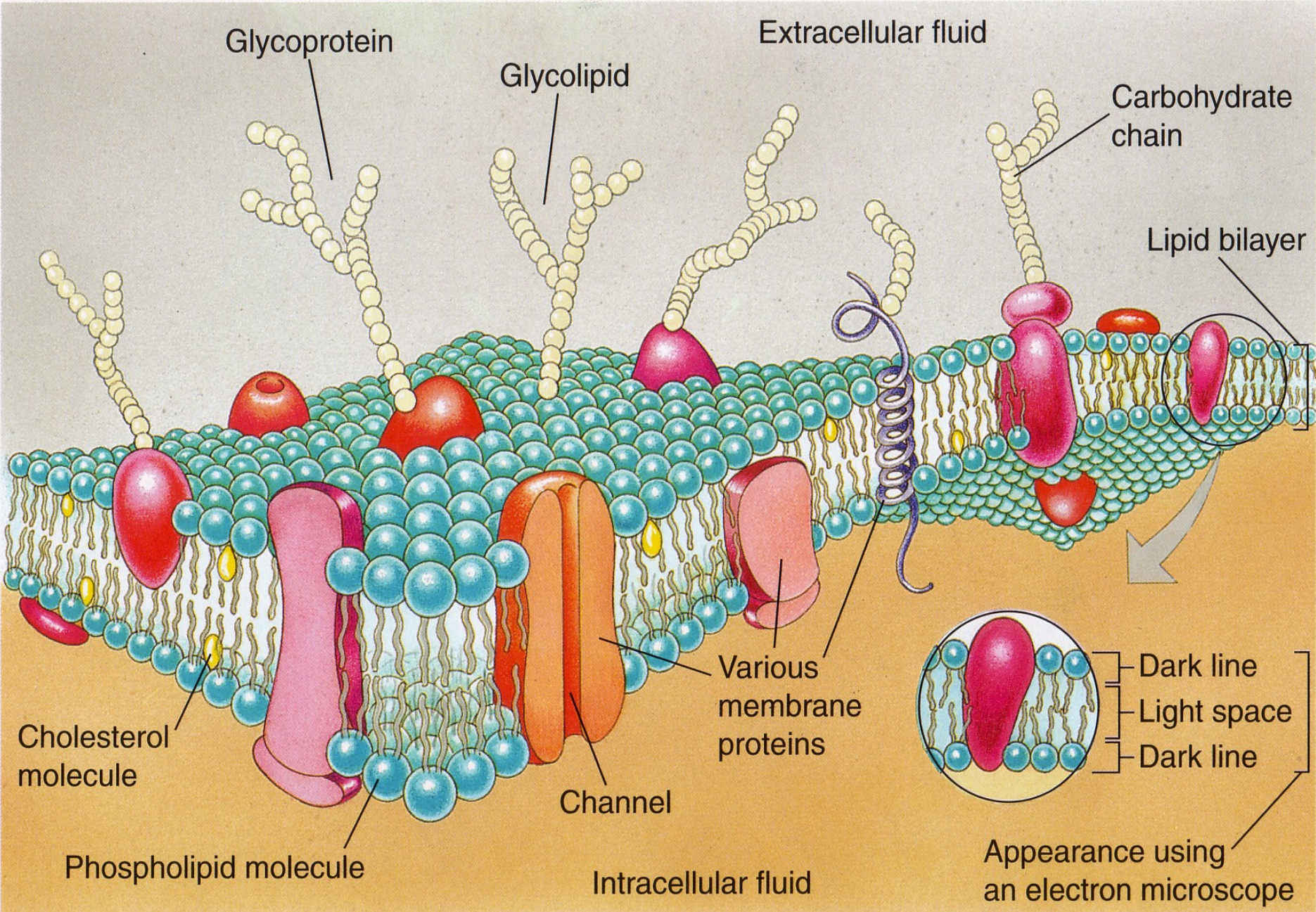
- Absorption
- Distribution (Where does the drug go?, storage?)
- Metabolism (Where and how is it broken down? Are the metabolites also active or toxic?)
- Excretion (How is the drug and its metabolites removed from the body?)
- Half life and duration of action

# ETHANOL

- **Chemistry:**  $\text{CH}_3\text{-CH}_2\text{OH}$
- **Absorption:** mostly intestines; also stomach and lungs
- **Metabolism:**



# Fluid Mosaic Model of Plasma Membrane Structure



**Table 1. Systemic Effects of Alcoholism**

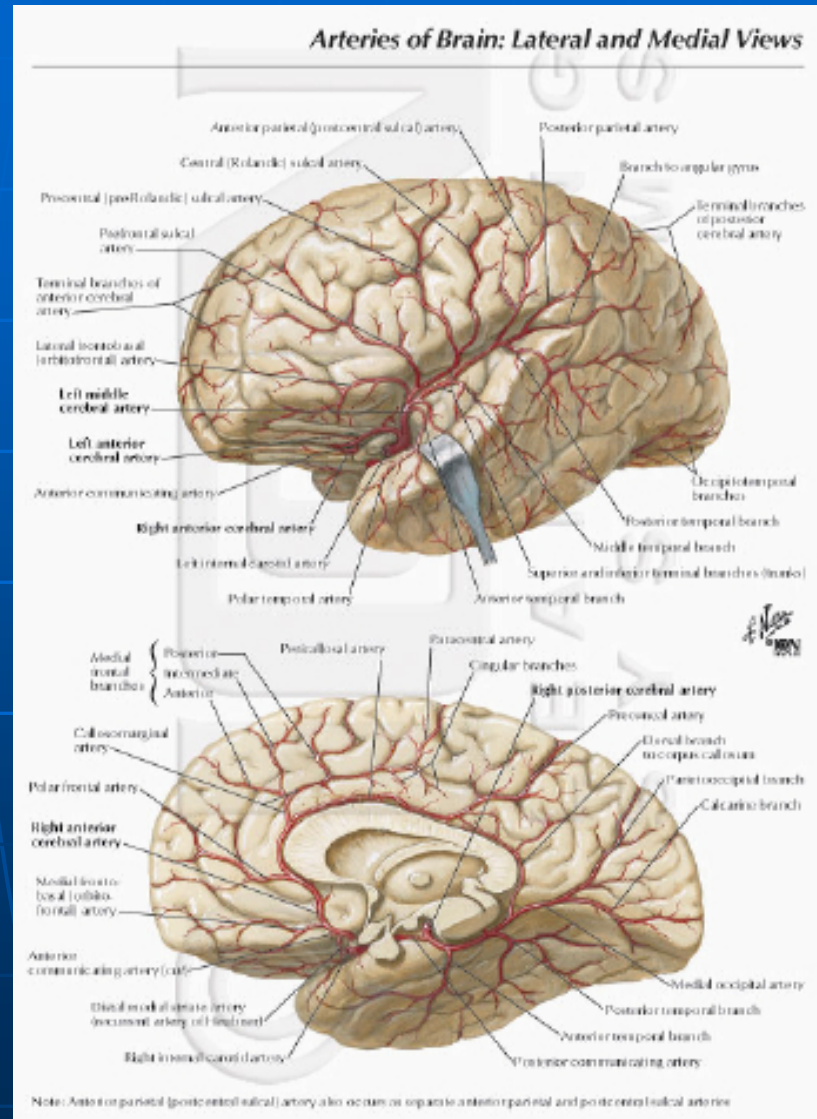
<b>Integument</b>	<b>Atelectasis</b>
Pellagra	Pneumothorax
Signs of trauma	Respiratory depression
Infestation	High prevalence of smoking
<b>Head</b>	<b>Cardiovascular</b>
Fracture	Cardiomyopathy
Subdural hematoma	Beriberi
Other trauma	<b>Genito-urinary tract</b>
<b>Mouth</b>	Hypogonadism (in men)
Nutritional stomatitis	Impotence (in men)
Cheilosis	Infertility (in women)
Increased incidence of cancers	<b>Endocrine and metabolic</b>
<b>Eyes</b>	Decreased testosterone
"Tobacco-alcohol" amblyopia	Hyperglycemia
Ophthalmoplegia (Wernicke-Korsakoff syndrome)	Hypoglycemia
<b>Gastrointestinal</b>	Hyperlactatemia
<b>Esophagus</b>	Hyperuricemia
Esophagitis	Metabolic acidosis
Diffuse esophageal spasm	Respiratory acidosis
Mallory-Weiss tear	Alcoholic ketoacidosis
Rupture with mediastinitis	Hypophosphatemia
Increased incidence of cancers	Hypermetabolism
<b>Stomach and duodenum</b>	Hypokalemia
Acute erosive gastritis	Hypomagnesemia
Chronic hypertrophic gastritis	Hypercholesterolemia
Peptic ulcer	Hypertriglyceridemia
Hematemesis	Protein malnutrition
Increased incidence of cancers	Hypotransferrinemia
<b>Bowel</b>	Vitamin B deficiencies
Malabsorption	<b>Neurologic</b>
"Alcoholic diarrhea"	Acute intoxication withdrawal syndromes
<b>Liver</b>	Amblyopia (optic neuropathy)
Steatosis	Wernicke-Korsakoff syndrome
Alcoholic hepatitis	Cerebellar degeneration
Cirrhosis	Polyneuropathy
<b>Pancreas</b>	Pellagra
Acute pancreatitis	Marchiafava-Bignami disease
Chronic recurrent pancreatitis	Central pontine myelinolysis
Calcific pancreatitis	Cerebral atrophy, dementia
Exocrine pancreatic insufficiency	Myopathy
Pseudocyst	
<b>Respiratory</b>	
Increased susceptibility to infection	
Fractured ribs	



# UGI Tract, liver, and pancreas



# Brain



# Fetal-Alcohol Syndrome

- Leading cause of mental retardation in western countries
- No known safe level of drinking during pregnancy
- Led to warning levels on alcoholic beverages



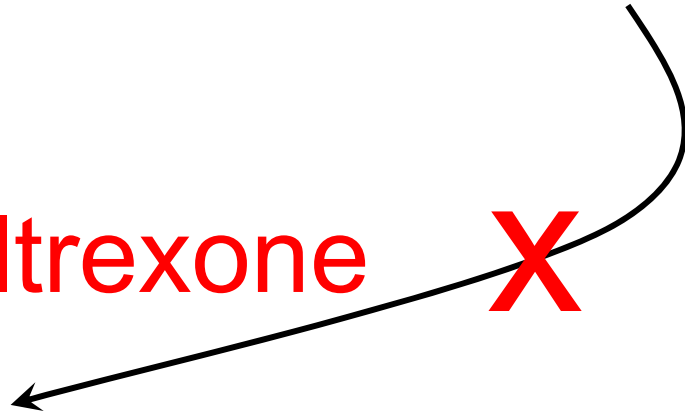
# Mechanism of action on the brain

- Triggers release of endorphins
- Membrane effect
- Interacts with GABA and glutamate receptors

Alcohol → Endorphins

Naltrexone X

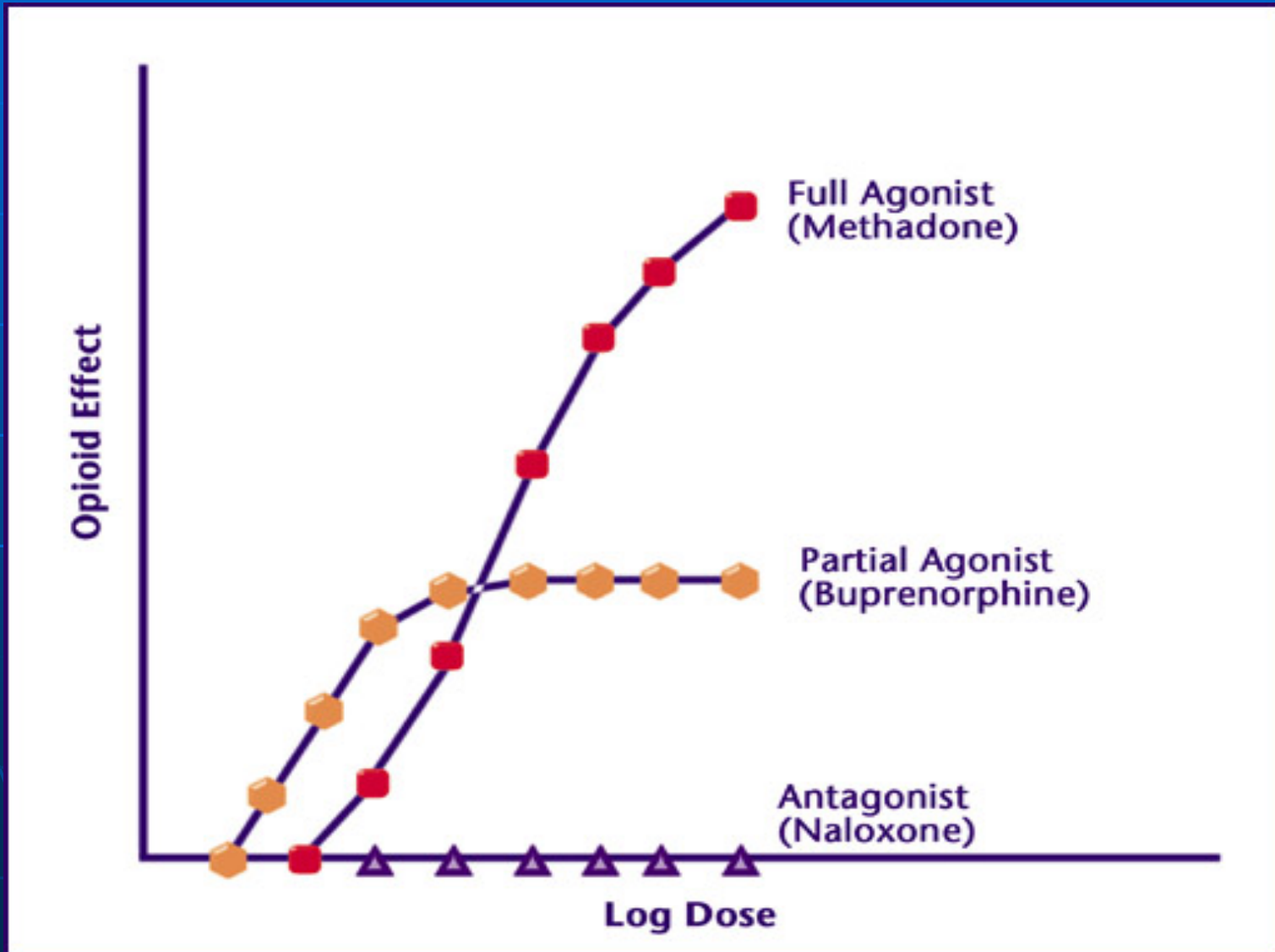
μ receptors → Euphoria



# Pharmacodynamics: The study of drug action in the body (especially drug-receptor interaction)

- Agonist: a drug that mimics the action of an endogenous chemical
- Partial agonist: a drug that works like an agonist but has a ceiling on its ability to stimulate a receptor
- Antagonist: a drug that blocks a receptor

# Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists\*



**Endorphins: endogenous + morphine**

**generic term referring to the 3 families of  
endogenous opioid peptides:**

**Enkephalins, Dynorphins & Endorphins**

# Endogenous opioids

Work to decrease the release of excitatory neurotransmitters (thus are natural tranquilizers)

- Endorphins
- Enkephalins
- Dynorphins

All work on different types of opioid receptors

- Mu (OP3)
- Delta (OP1)
- Kappa (OP2)

# Opioids

- Very effective for analgesia
- Major toxicity due to impurities, needle use, and illegal behavior necessary to gain resources to purchase drug
- In pure form very addictive but not especially toxic

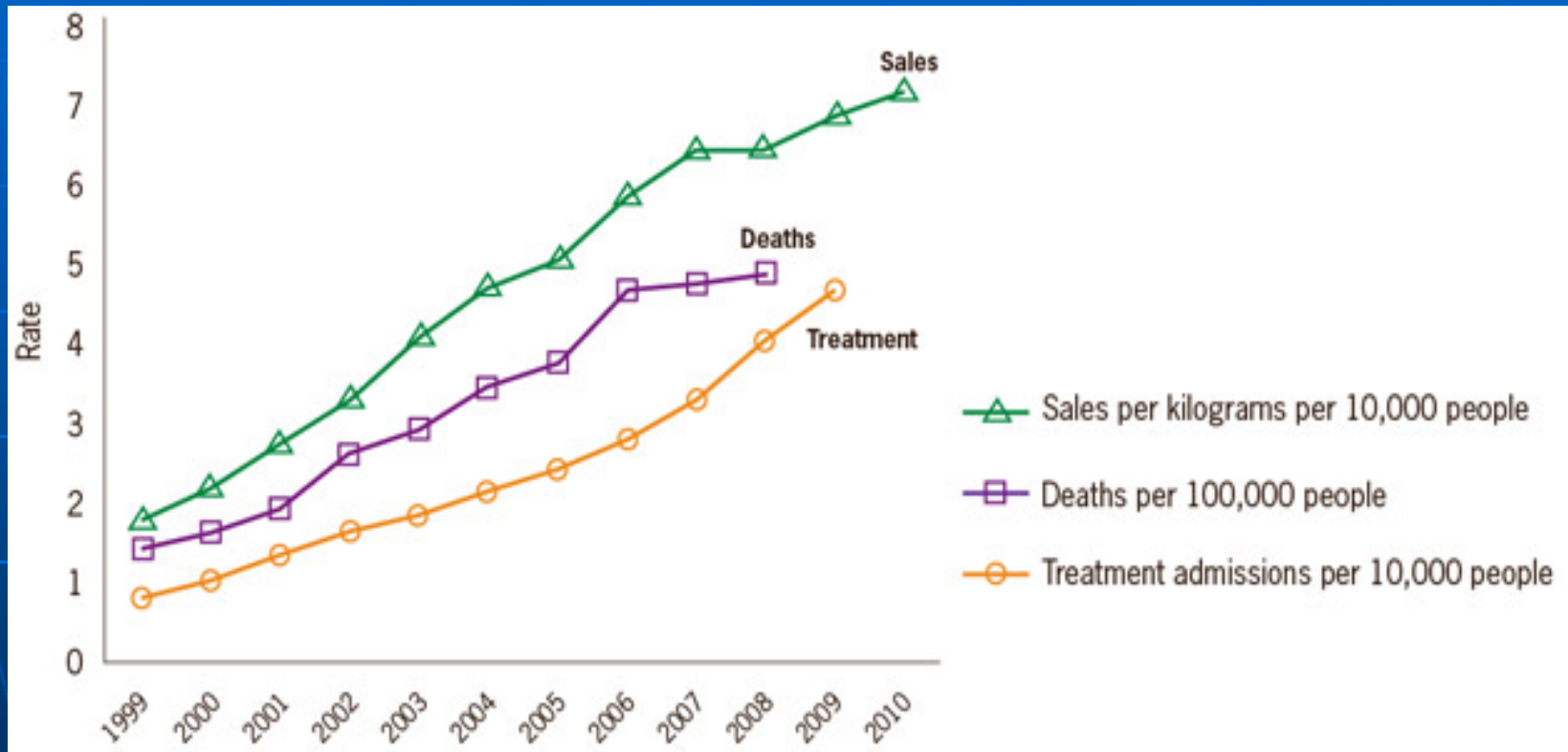
# Abuse and Use of Opioids

- Heroin: to get high
- Morphine and others: for pain relief
- Methadone and buprenorphine: to treat opioid dependency
- Naloxone: to treat opioid overdose
- Naltrexone: to treat alcoholism



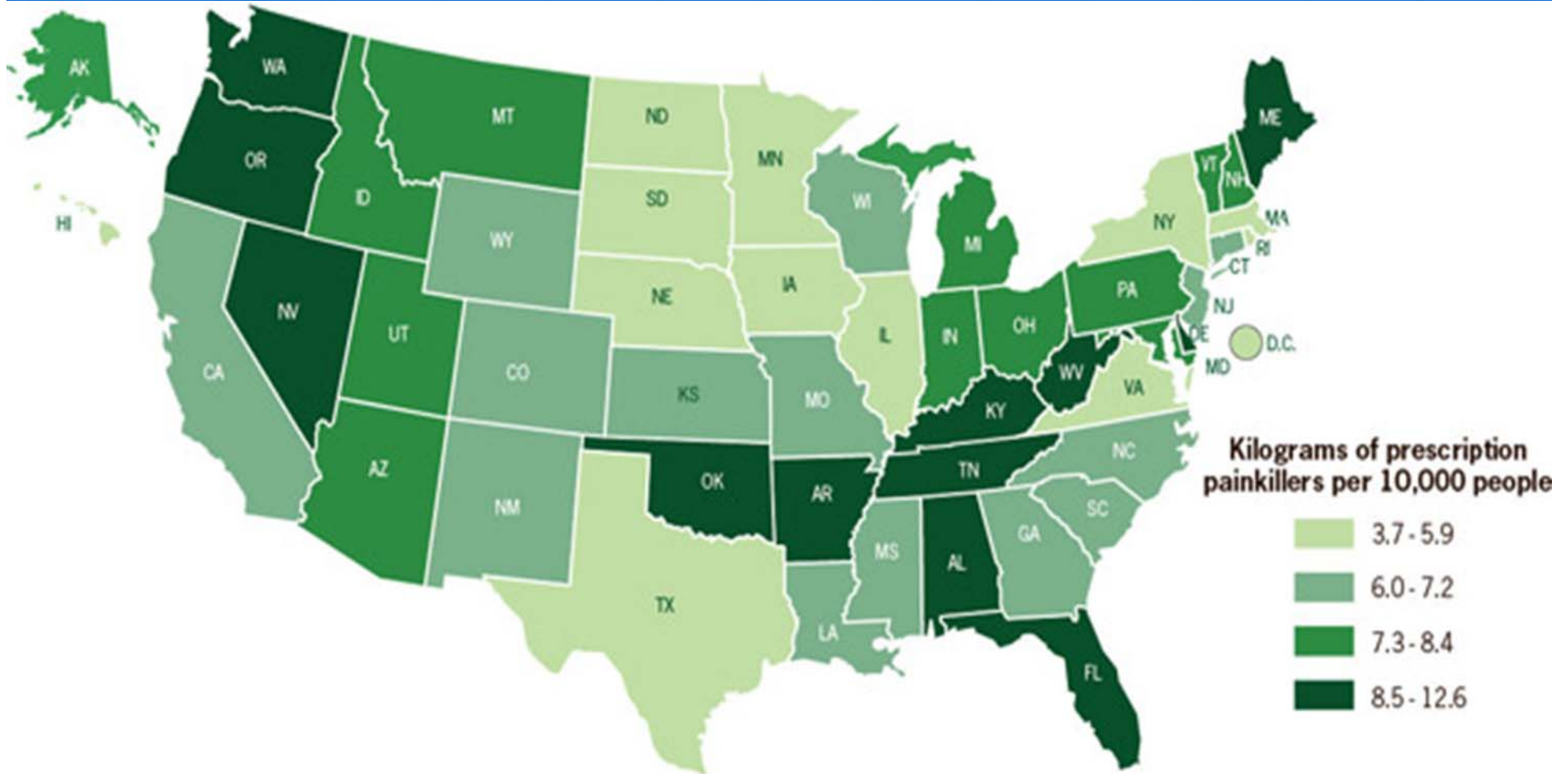
# Prescription Drug Abuse

- 2010: about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the past year.
- 1997-2007: 74mg/person opioid to 369mg/person, increase of 400%.
- 2000-09: 1,200 Overdose deaths in OR due to prescription pain killers.
- Prescription painkiller overdoses killed nearly 15,000 people in the US in 2008. This is more than 3 times the 4,000 people killed by these drugs in 1999.



# Prescription painkillers sold by state per 10,000 people (2010)

SOURCE: Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 2010



# Affinity and Dissociation

- Affinity:

Strength with which a drug binds to its receptor

(Strength of binding is not related to activation or efficacy at the receptor)

- Dissociation:

Speed (slow or fast) of disengagement or uncoupling of drug from the receptor

# Affinity and Dissociation

**Buprenorphine** has:

- high affinity for mu opioid receptor-competes with other opioids and blocks their effects
- slow dissociation from mu opioid receptor
- prolonged therapeutic effect for opioid dependence treatment

# Buprenorphine Summary

- Buprenorphine a partial mu agonist opioid with high affinity and slow dissociation thus also acts as exogenous opioid blocker
- Profile of effects similar to other mu agonist opioids, but less risk of respiratory depression, lower level of physical dependence
- Can be abused, but combination with naloxone decreases abuse potential

# JH, 32yo man

- Consult this weekend at local hospital.
- Grew up in drug using and dealing home and started MJ and EtOH as teen.
- Married, separated, homeless for 2 yrs.
- 9<sup>th</sup> grade education, GED, and worked on poultry farm for 10yrs but lost job due to amphetamine use.
- Later turned to heroin and recently ½ g/d IV
- Admitted New Years Eve to hospital due to severe fatigue.

# JH Continued

- Found to have MRSA bacteremia
- Getting better on antibiotics
- Wants help with his addiction.
- Started on Suboxone and quickly stabilized.
- Intends treatment program along with continuing the Suboxone.

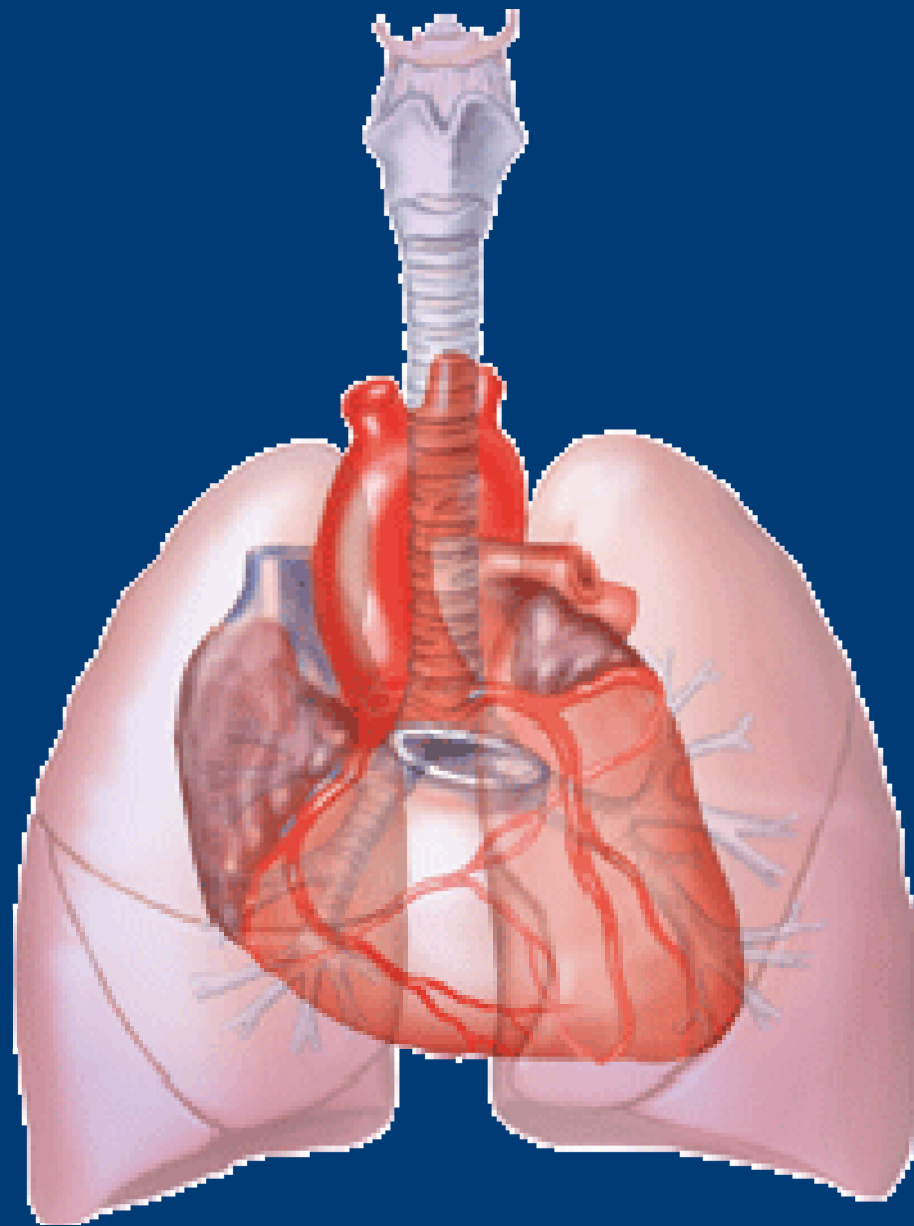


# Ally, now 26yo woman

- U/O student, single, smoker
- Problems with alcohol age 16 including crashed car
- Age 17 started using OxyContin
- Switched to heroin snorting then IV
- Consult 8/08, age 20

# Ally, Continued

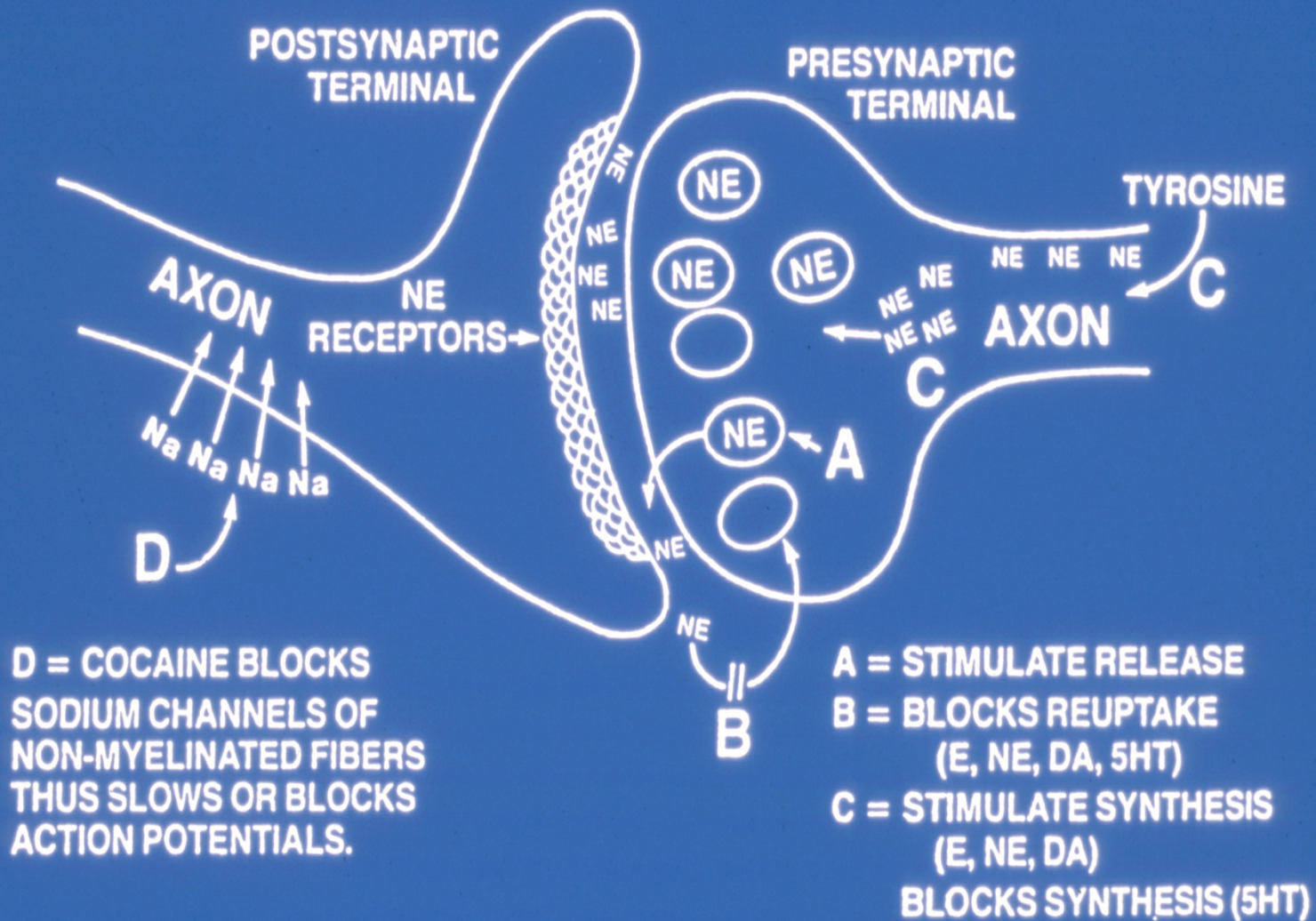
- 2008, Started on buprenorphine 4mg
- No other opioids since on buprenorphine
- 7/09, Started taper with decrease to 3mg
- Summer, 2009, quit smoking
- 10/09, decreased to 2mg
- 11/09, decreased to 1mg
- 1/10 stopped—had mild withdrawal



# Neurosynapse and Neurotransmitters

**The structures and chemicals that allow one nerve cell to communicate with another**

# COCAINE'S LOCAL ANESTHETIC AND SYMPATHOMIMETIC EFFECTS



# Cocaine and Amphetamines: Stimulants of the central nervous system

- Increase blood pressure
- May increase or decrease pulse
- Increase body temperature
- Dilate pupils

## Stimulants:

cocaine, amphetamines, and others

- Cocaine: formally used as local anesthetic
- Amphetamines and others: effective for attention deficit disorder (e.g. methylphenidate) and sometimes used for weight loss
- Potentially very toxic to CNS and heart
- May cause psychosis
- Intranasal use causes nose damage

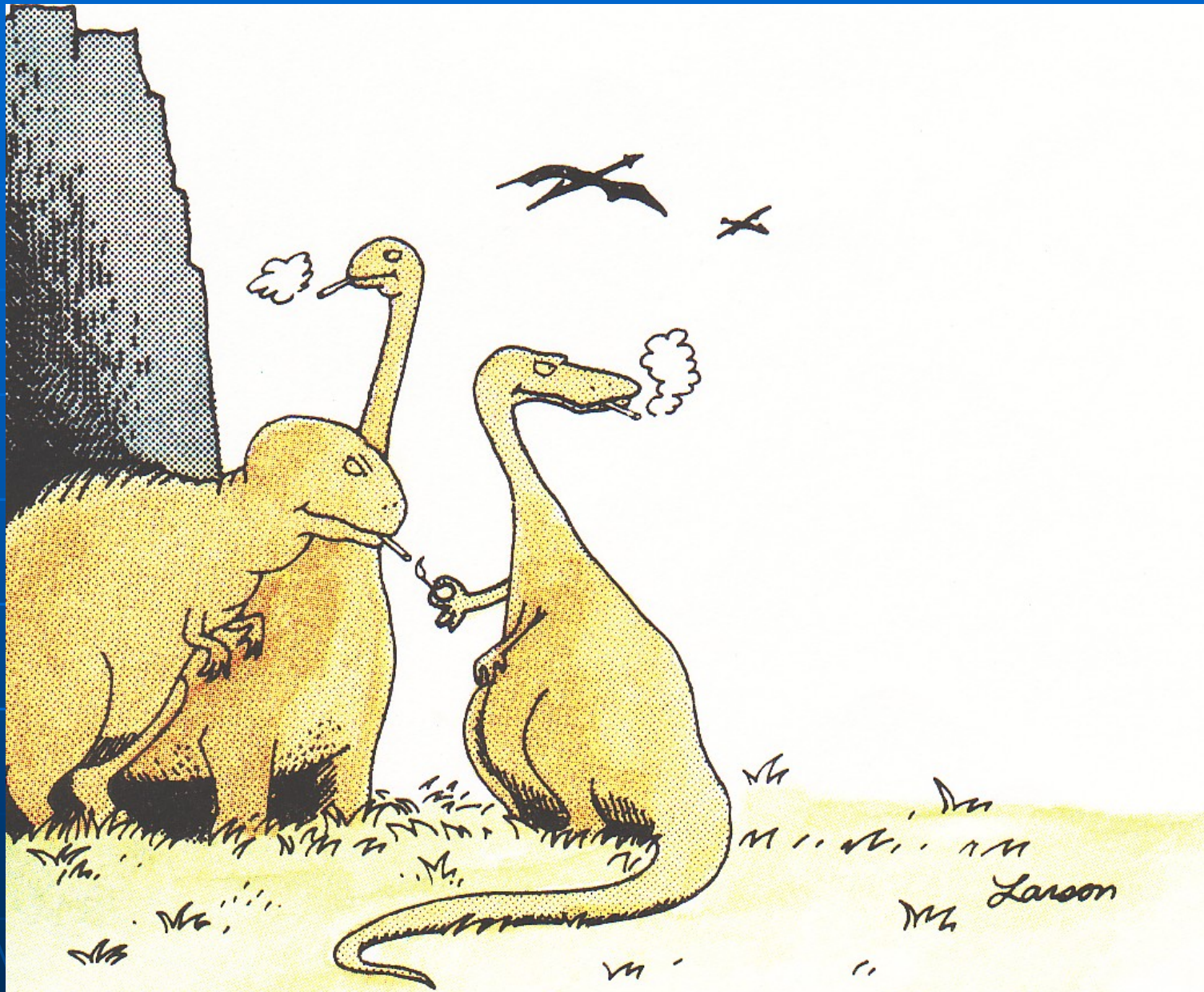
# Pharmacokinetics of Drugs of Addiction

## Drug delivery: process and systems

- Oral (usual stomach transit time about 1 hr.)
- Parenteral: IV, IM, and subcutaneous
- Inhalation (i.e. smoking)
- Transmucosal (i.e. snorting, sublingual)
- Transdermal (e.g. patches and gels)



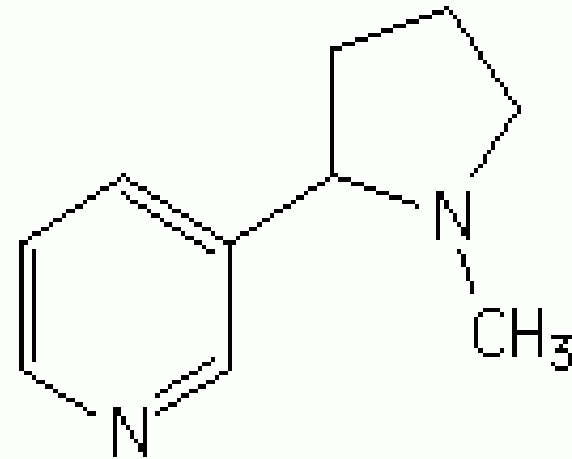




**The real reason dinosaurs became extinct**

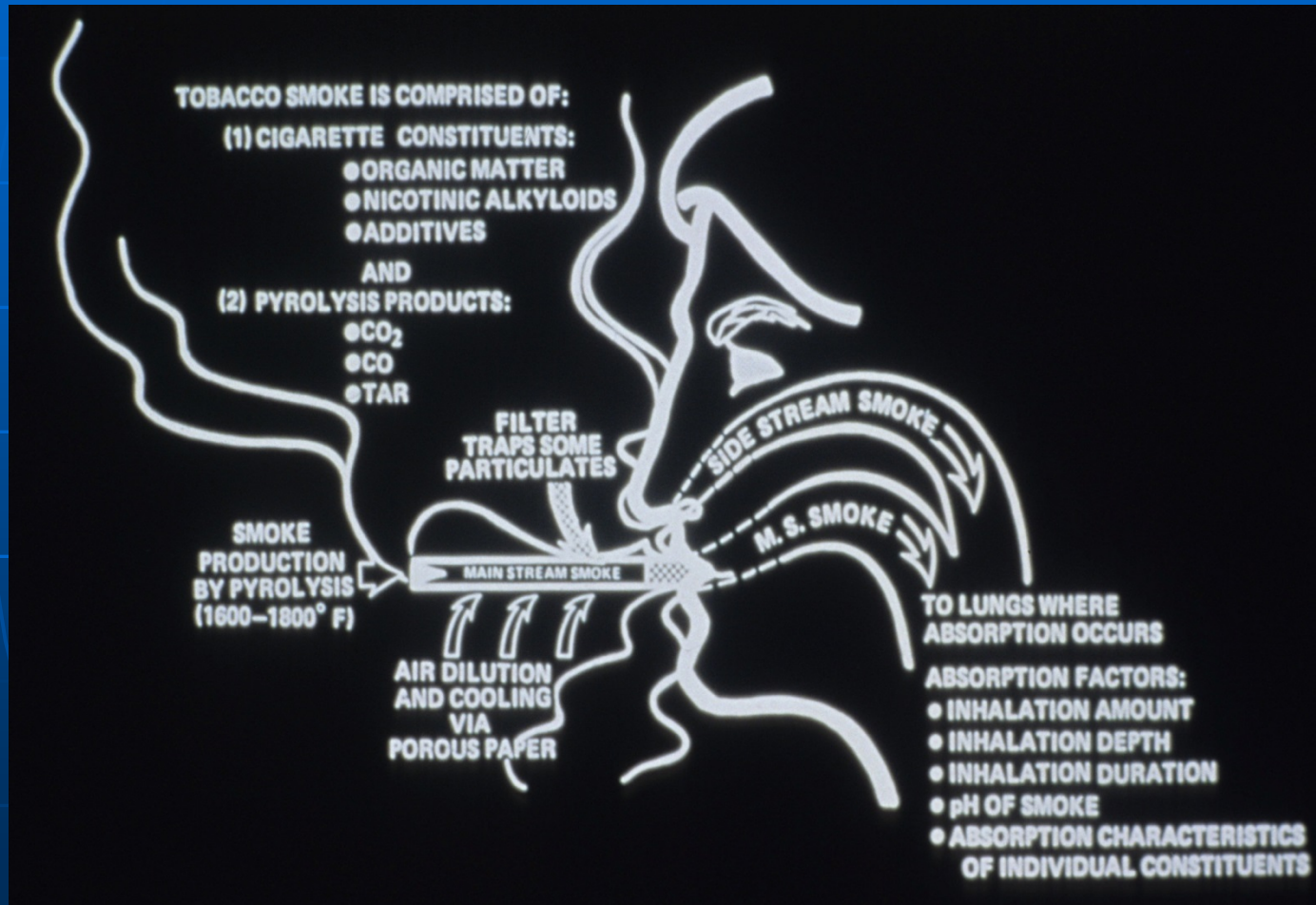
# Nicotine

- Not especially toxic but very addictive
- Usually delivered by smoking tobacco
- Tobacco smoke with over 4000 chemicals— at least 50 are known carcinogens
- Tobacco smoking is leading preventable cause of death in USA

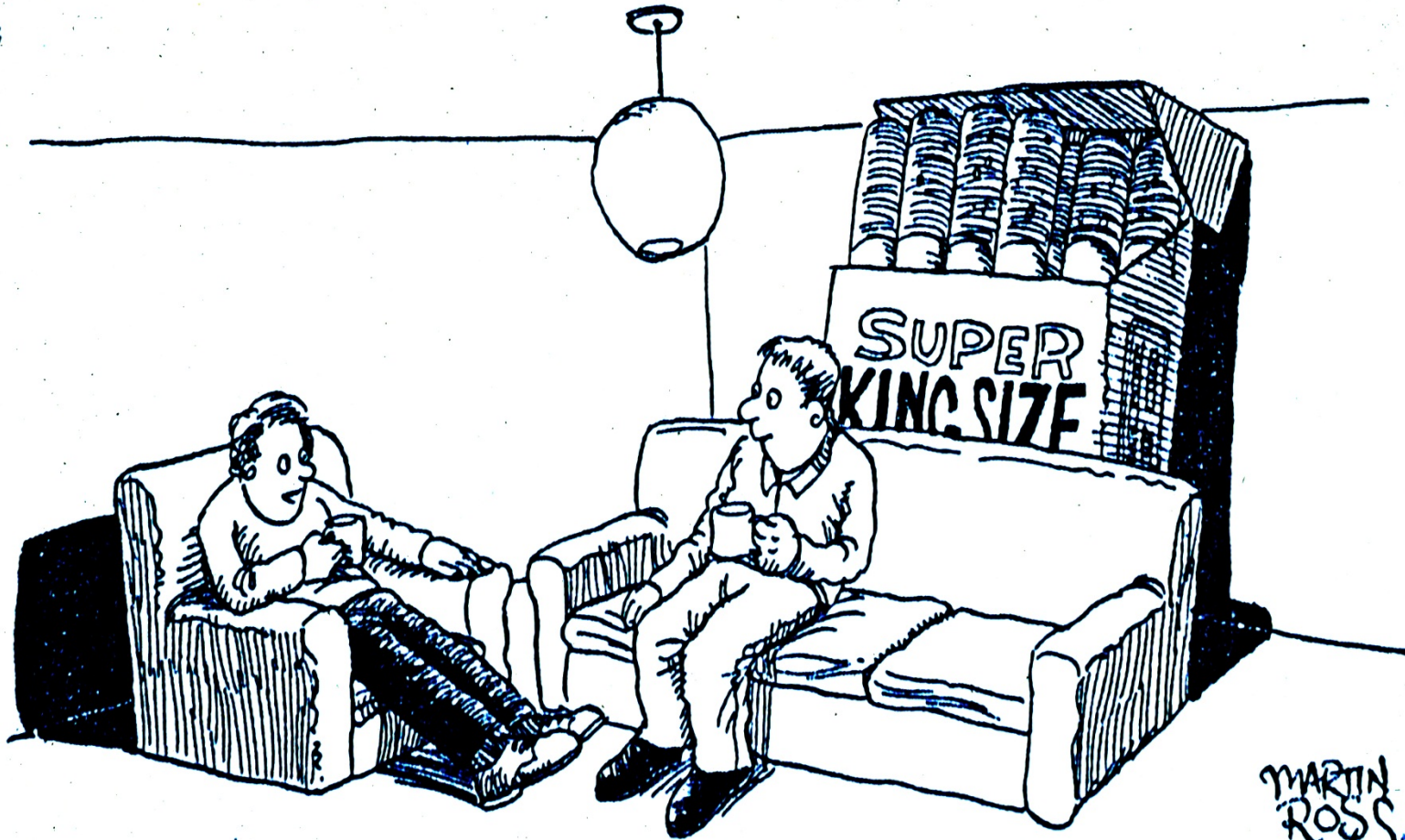


Nicotine

# Absorption & Fate of Cigarette Smoke



© FUNGI



MARTIN  
ROSS

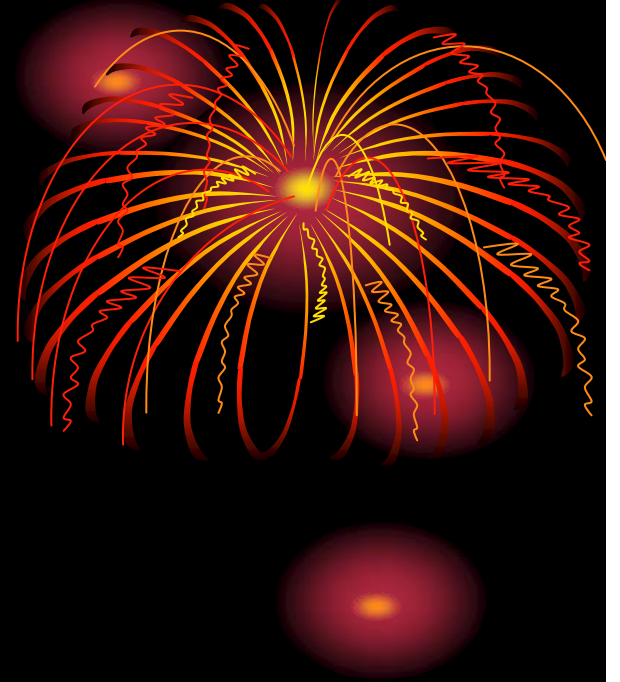
*“I was smoking 40 a day, but now  
I’m down to just two.”*

# Marijuana/THC

- Works on CB1 (most common receptor in the brain) and CB2 receptors (mostly on immune cells).
- Impairs learning, judgment, and reaction time (Recent studies show early onset marijuana smokers demonstrate significantly worse performance on cognitive tasks and the effect is dose related).
- Effective for appetite stimulation, spasticity, nausea, and pain

# Endocannabinoids

- Anandamide and 2-arachidonylglyceride (2AG)
- Cells release chemicals locally and interact with local cells (paracrine system)
- Action on CB-1 receptors leads to net anabolic action (i.e. net increase in energy intake and storage).
- Includes: Stimulates food intake, increases storage of fat, stimulates the liver to increase de-novo synthesis of fatty acids, and reduces sensation of satiety.



- QUESTIONS



# *Endocannabinoid Receptors*

## **CB-1**

Brain Structures

Controlling Energy  
Intake

(eg, Hypothalamic  
Hunger-Satiety Center)

Endocannabinoid  
hyperactivity →

## **CB-2**

Leukocytes/WBCs

Immune & Inflammatory  
Reactions

(eg, Lymphocytes &  
Macrophages)

Metabolic & Eating Disorders

1. Abdominal Obesity
2. Dyslipidemia
3. Hyperglycemia

<http://www.jimmunol.org/content/165/1/373.full?ijkey=YriEsKcvAs2z>

# Casey

- Late 30s yo man, married, works full time for sporting goods company
- Hx of smoking heroin many yrs ago
- Hx of kidney stones and anxiety disorder
- Was using Percoset, morphine, Dilaudid, or OxyContin up to **40 tablets/day**
- 10/03, Detoxed at Buckley House
- 10/03, Serenity Lane residential TX

# Casey, 2004

- Relapsed to high dose oral opioids
- 6/04, admitted to opioid agonist treatment program (IHC) using methadone
- Dose up to 80mg to help with anxiety as well as addiction
- Tapered down to 35mg over 3mo.
- 2/15/05, Suboxone induction done

# Casey on buprenorphine

- 2/17/05, c/o diarrhea, cold, chills, rhinorrhea, antsy
- Dose increased up to 32mg over the next month
- 4/12/05, Feels "normal" and "got stabilized" Says "grateful" for med
- Now on 16mg/d after slow taper. Feeling well and doing well with family and work.