

DRUGS OF ADDICTION:

A Survey of their Pharmacology
& Pathophysiology

Douglas L. Bovee, MD, FACP

Addiction Medicine Specialist

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BACKGROUND:

Douglas L. Bovee, MD

- Pharmacy and pharmacology background
- Medical school
- Residency in Internal Medicine
- Adult primary care
- Addiction Medicine: diagnosis, treatment and referral of drug dependent patients, 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

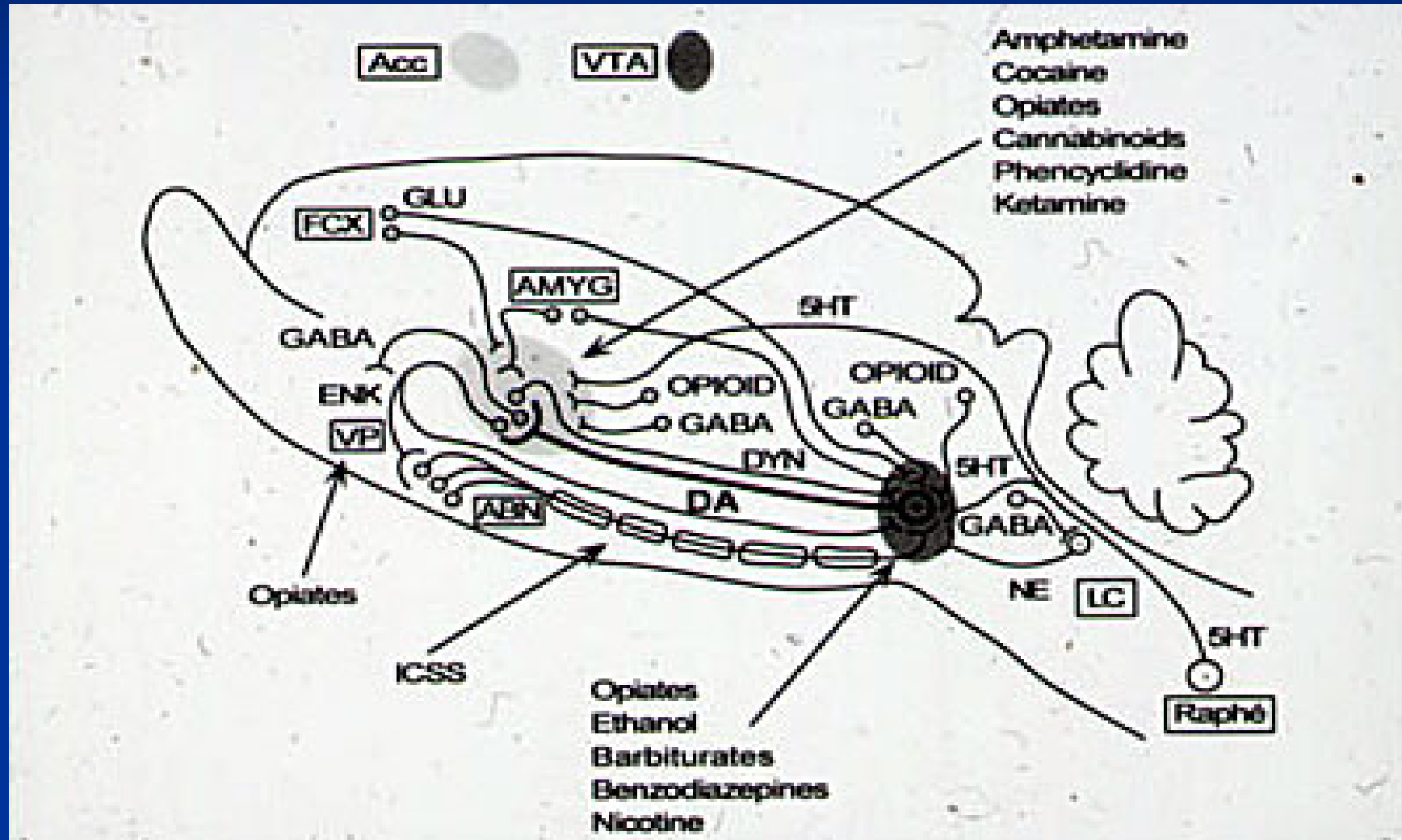
A disease characterized by continuous or periodic:

- 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

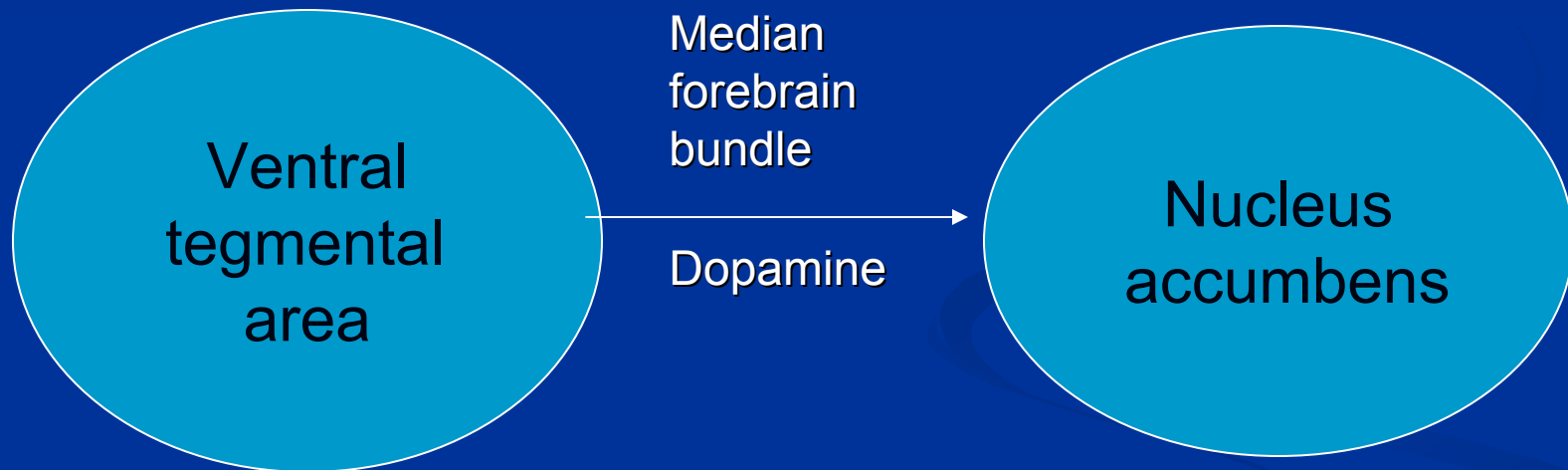
- Loss of control
- Craving and compulsion
- Continued use despite adverse consequences

Reward center



Reward Pathway

This system is activated by drugs of abuse

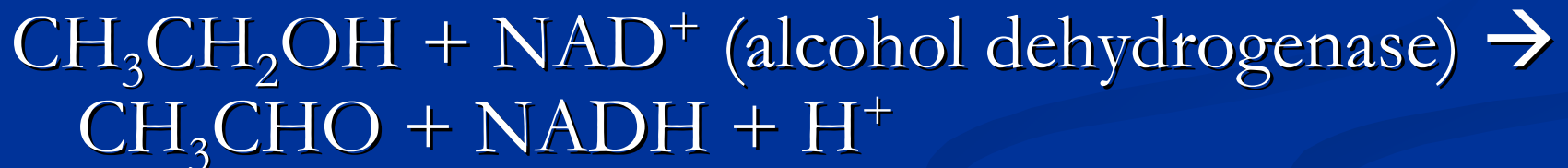


Pharmacokinetics: the study of the movement of a drug thru the body

- 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

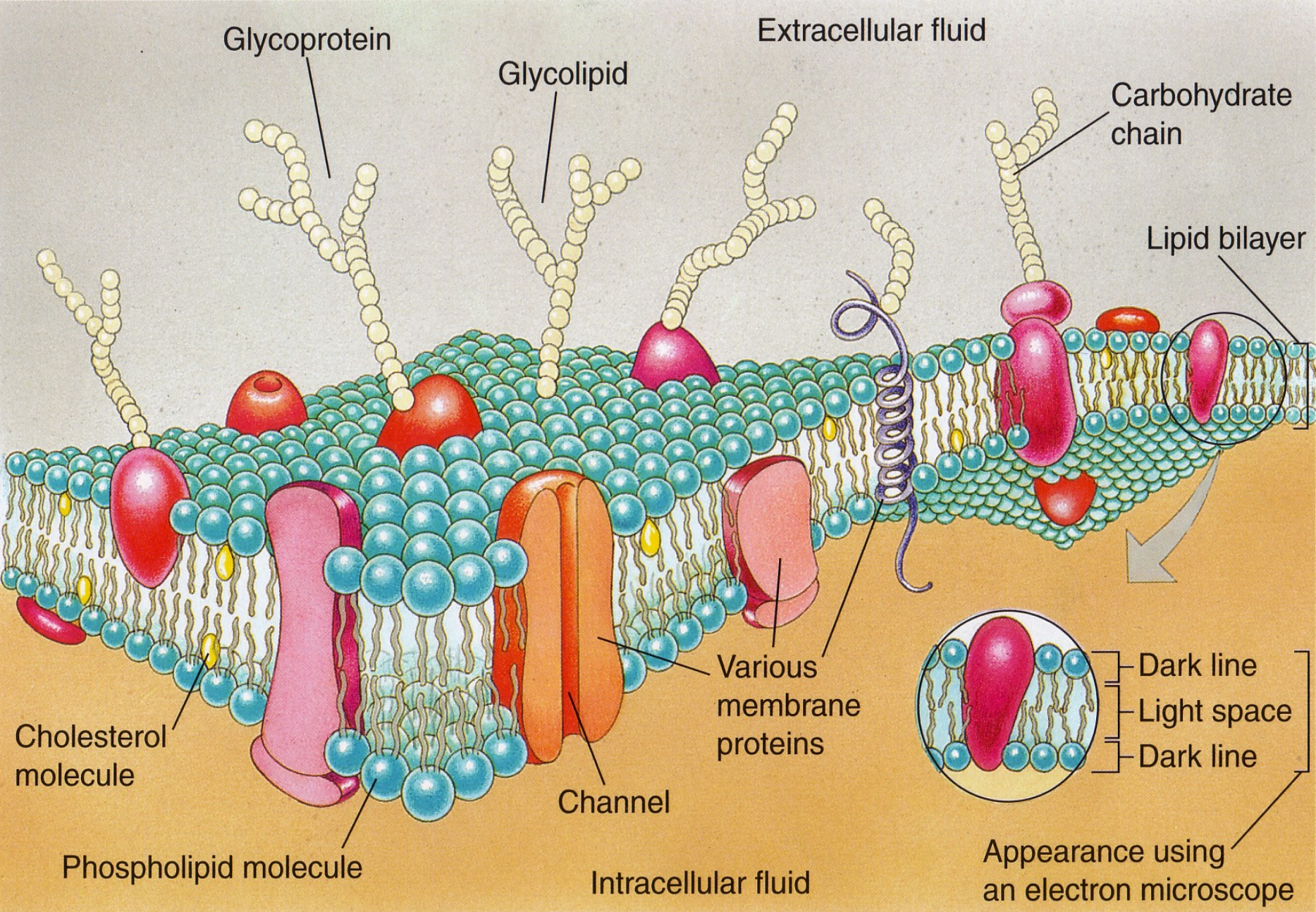
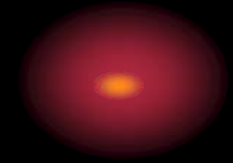
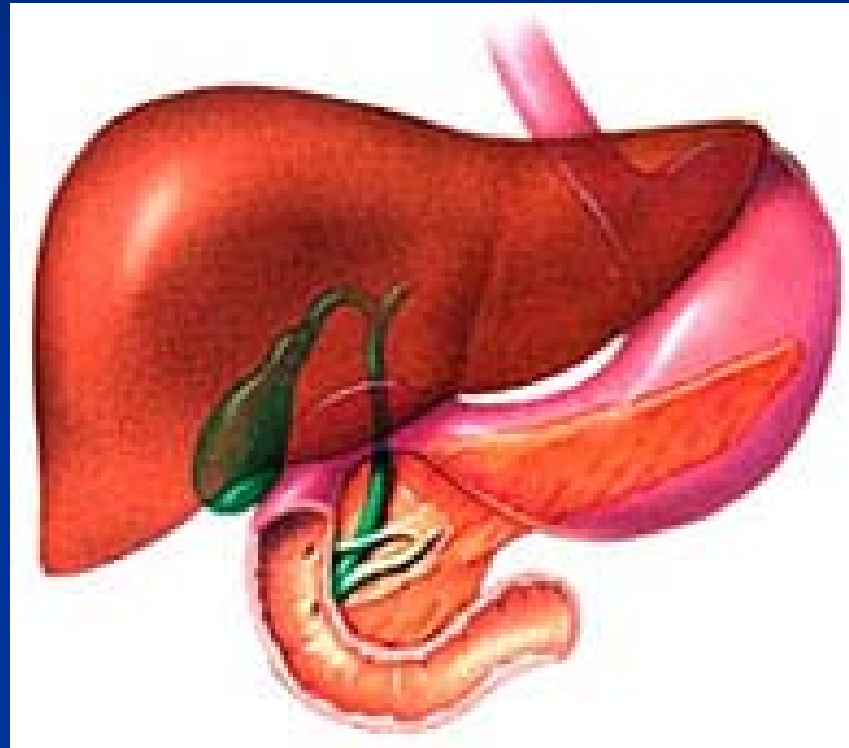


Table 1. Systemic Effects of Alcoholism

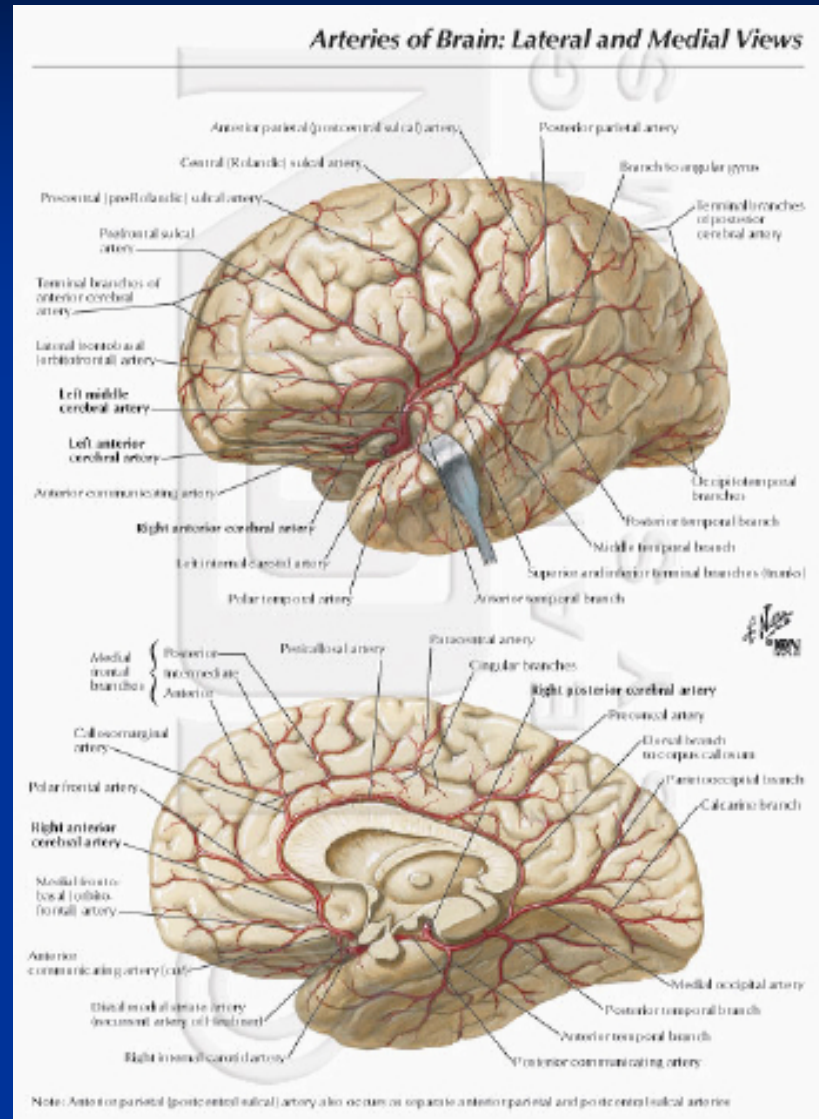
Integument	Atelectasis
Pellagra	Pneumothorax
Signs of trauma	Respiratory depression
Infestation	High prevalence of smoking
Head	Cardiovascular
Fracture	Cardiomyopathy
Subdural hematoma	Beriberi
Other trauma	Genito-urinary tract
Mouth	Hypogonadism (in men)
Nutritional stomatitis	Impotence (in men)
Cheilosis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

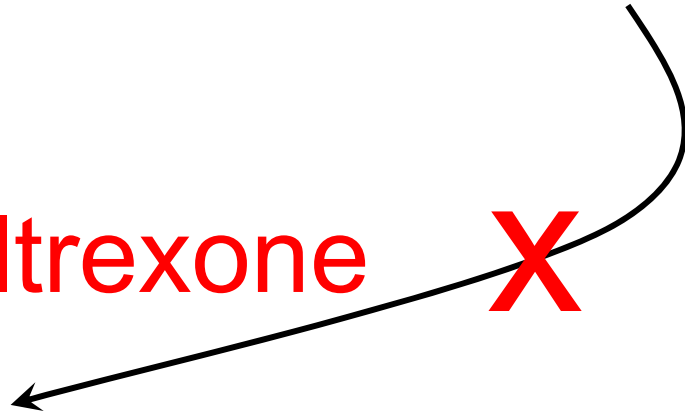
Mechanism of action on the brain

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

Alcohol → Endorphins

Naltrexone X

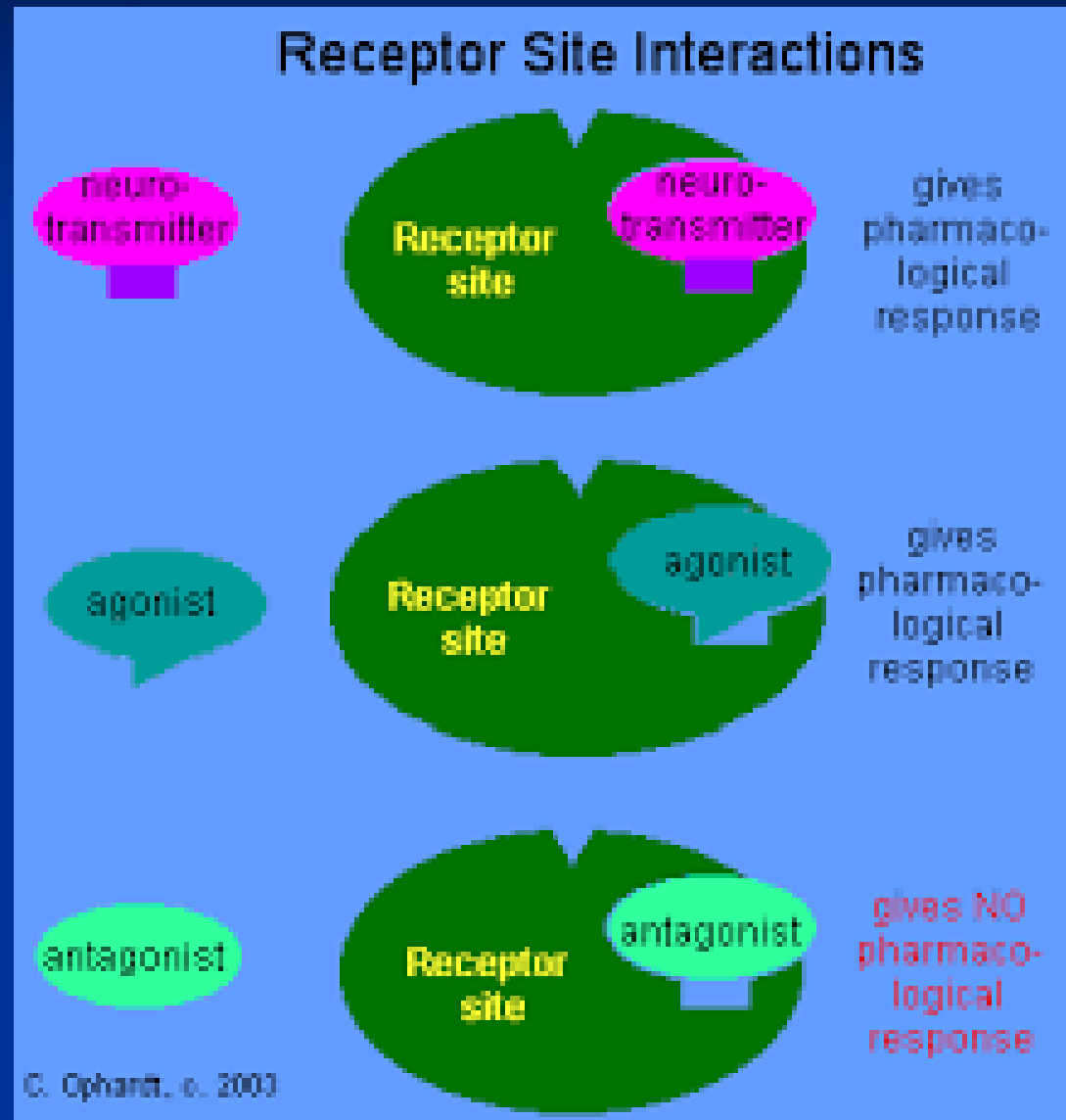
μ receptors → Euphoria



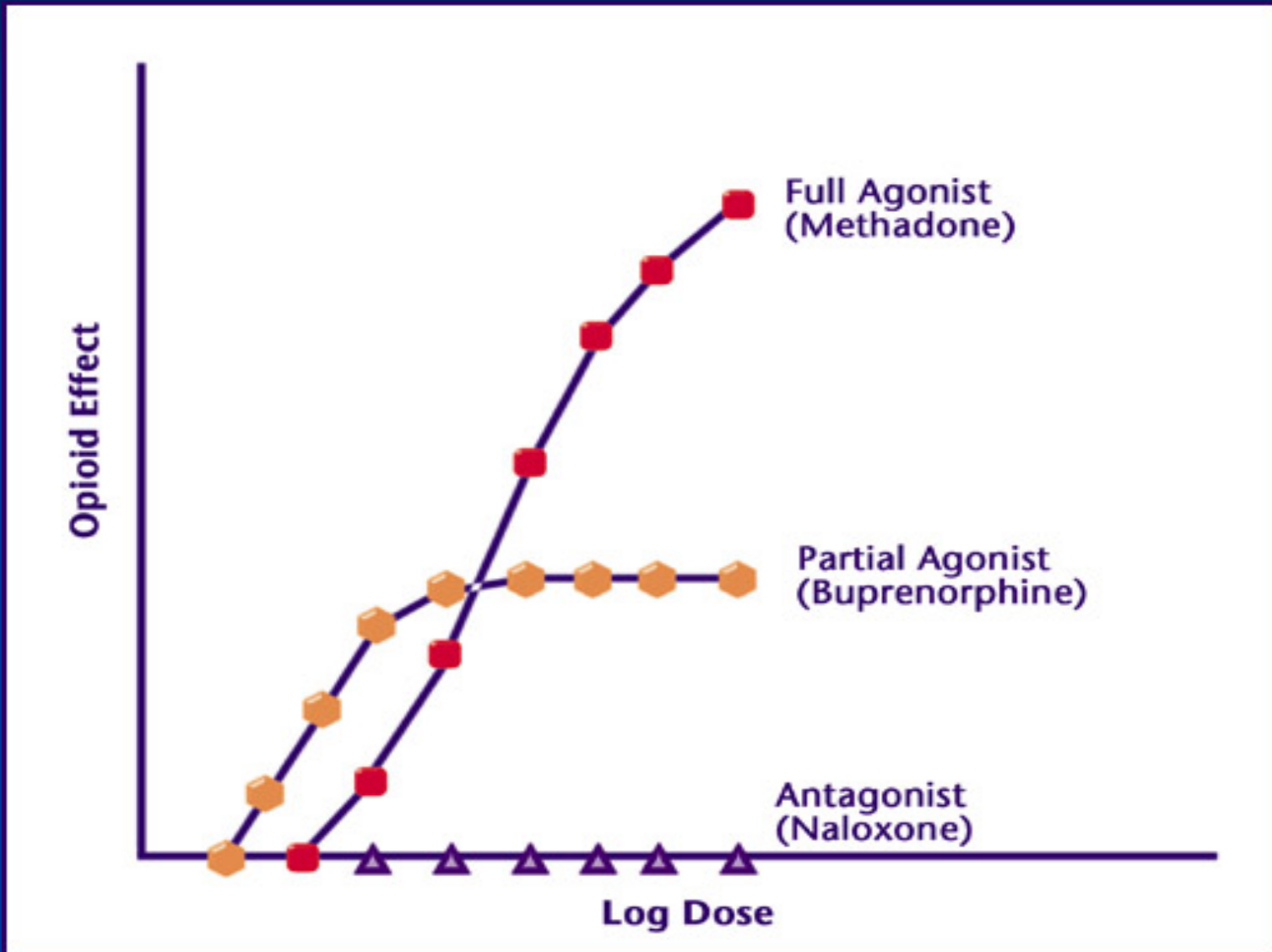
Pharmacodynamics: The study of drug action in the body (especially drug-receptor interaction)

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

Drug- Receptor Coupling



*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.

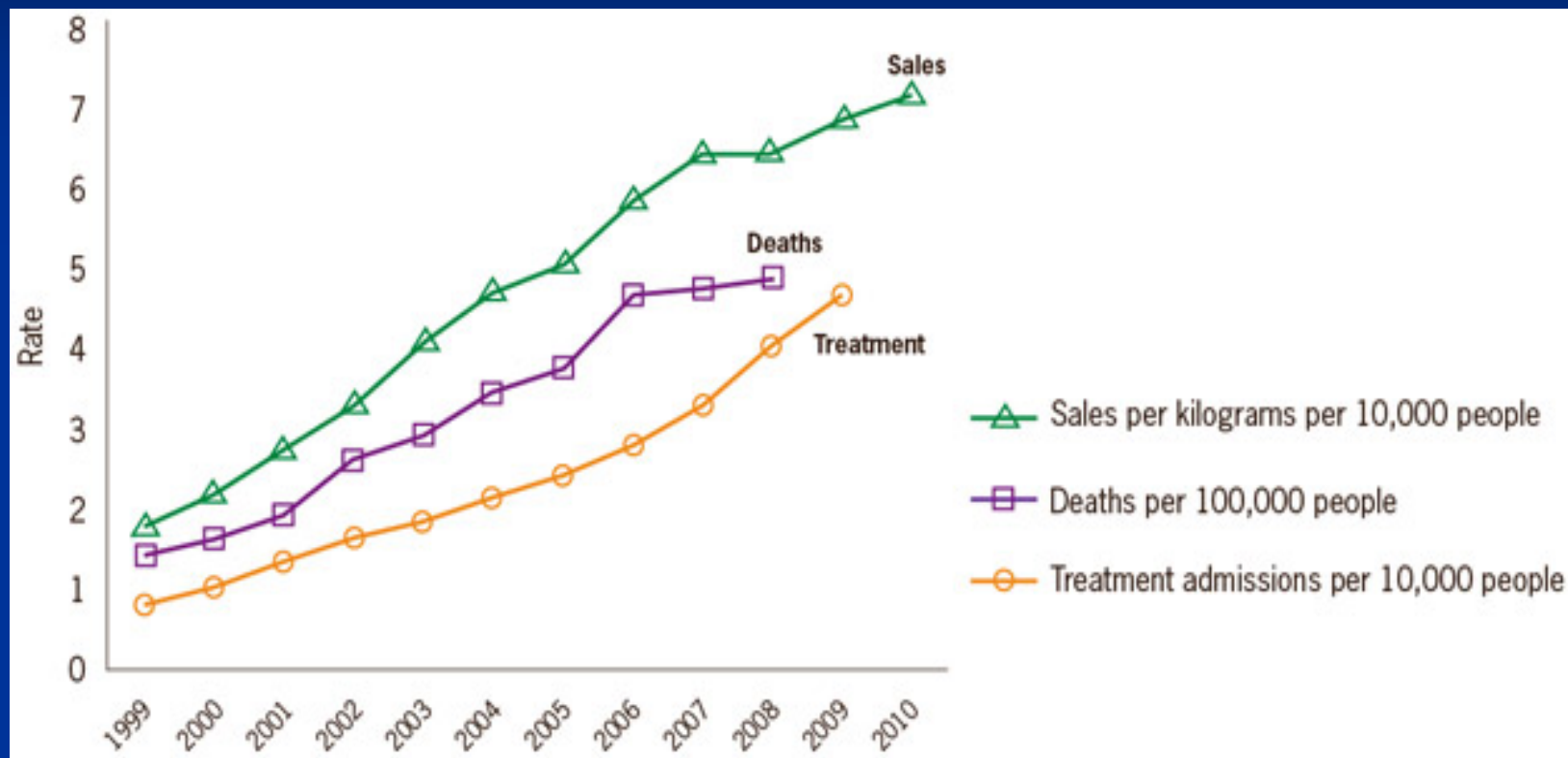
Abuse and Use of Opioids

- 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.

Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

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

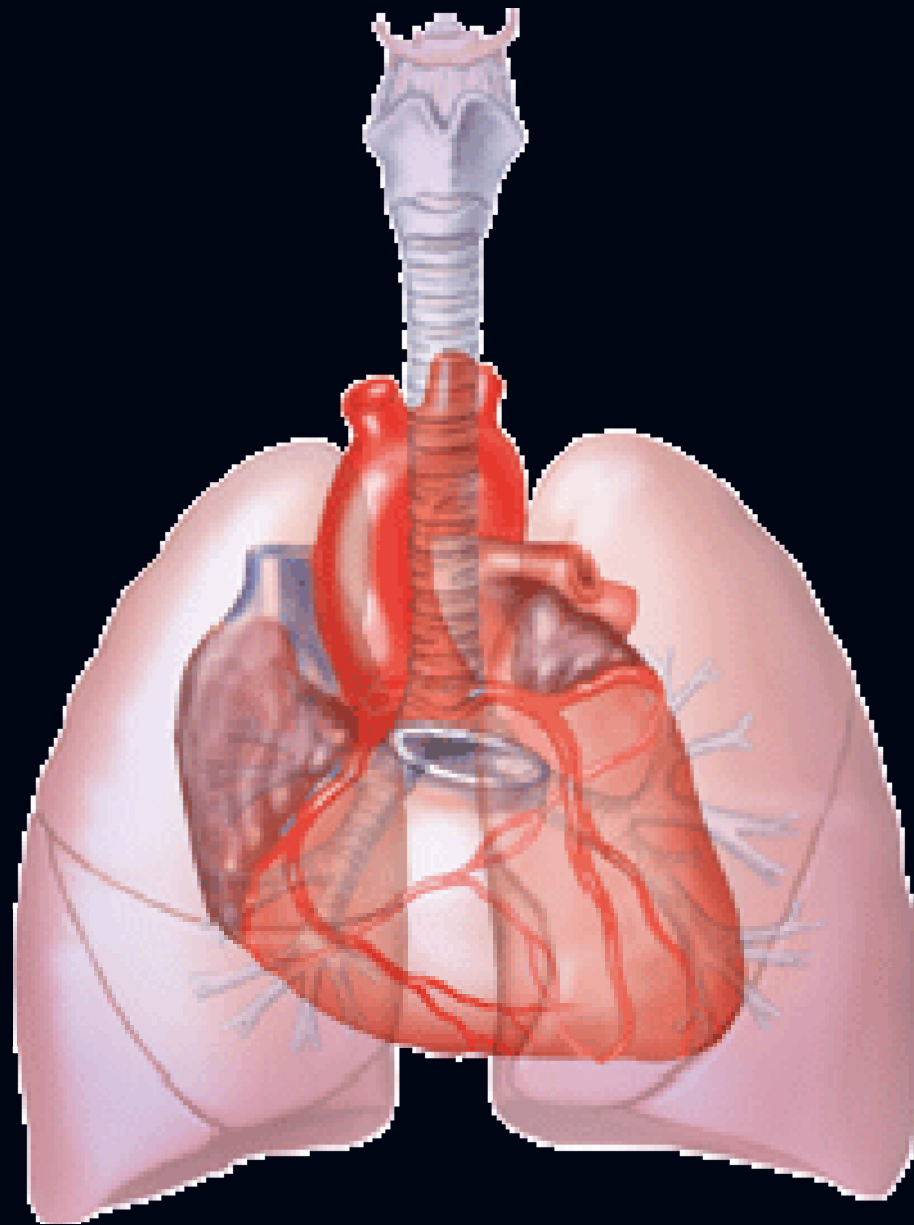
- Buprenorphine a partial mu agonist opioid with high affinity and slow dissociation thus also acts as exogenous opioid blocker
- Profile of effects similar to other mu agonist opioids, but less risk of respiratory depression, lower level of physical dependence
- Can be abused, but combination with naloxone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

JH, 33yo man

- Consult last year at local hospital.
- Grew up in drug using and dealing home and started MJ and EtOH as teen.
- Married, separated, homeless for 2 yrs.
- 9th grade education, GED, and worked on poultry farm for 10yrs but lost job due to amphetamine use.
- Later turned to heroin and recently 1/2 g/d IV
- Admitted New Years Eve to hospital due to severe fatigue.

JH Continued

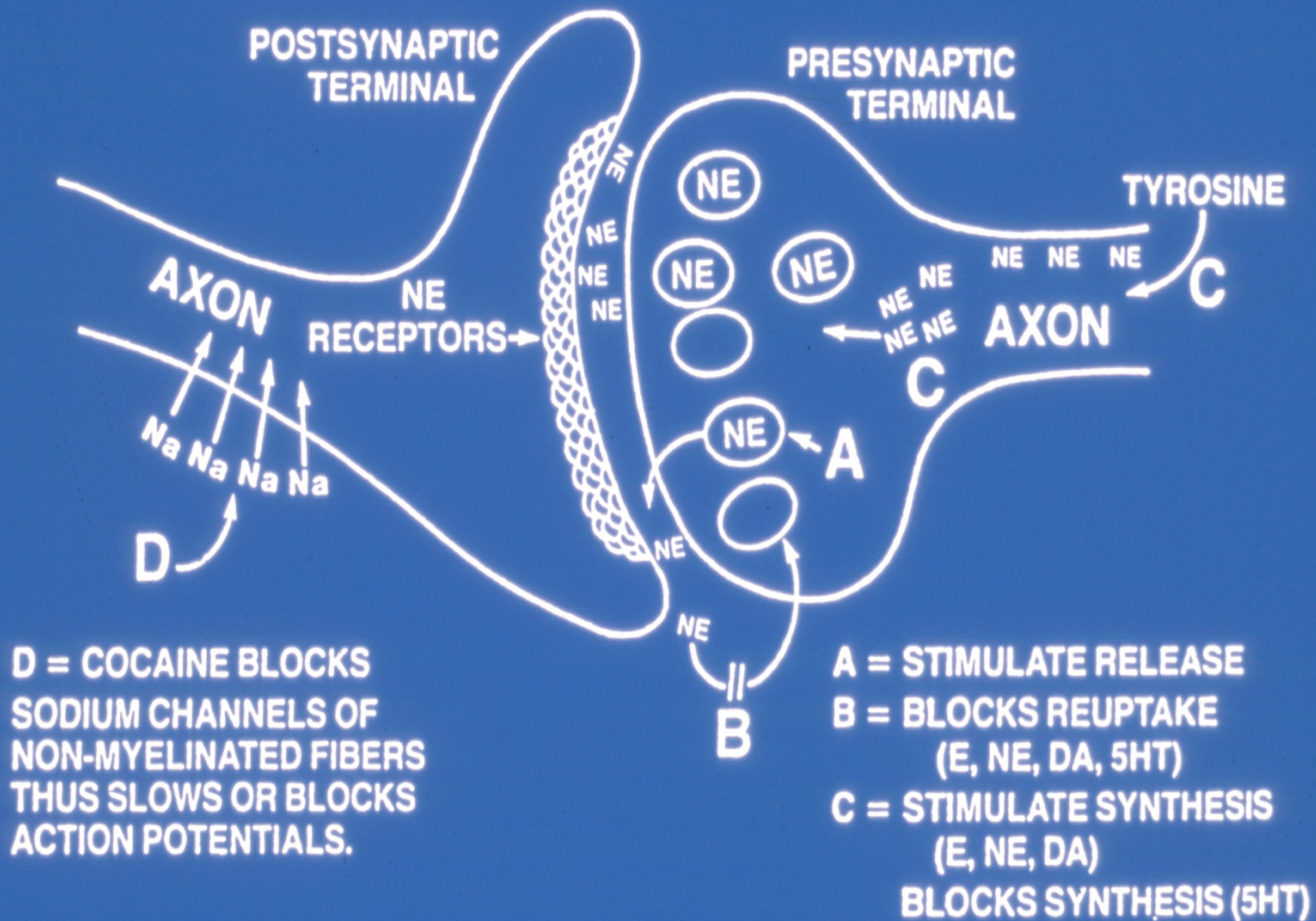
- Found to have MRSA bacteremia.
- Recovered with antibiotic treatment.
- Wanted help with his addiction.
- Started on Suboxone and quickly stabilized.
- 1 yr later much improved on Suboxone with greatly reduced drug use and no hospitalizations.
- Still homeless but looking for work.
- Says going to 12 step meetings.



Neurosynapse and Neurotransmitters

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

COCAINE'S LOCAL ANESTHETIC AND SYMPATHOMIMETIC EFFECTS



D = COCAINE BLOCKS SODIUM CHANNELS OF NON-MYELINATED FIBERS THUS SLOWS OR BLOCKS ACTION POTENTIALS.

A = STIMULATE RELEASE
B = BLOCKS REUPTAKE (E, NE, DA, 5HT)
C = STIMULATE SYNTHESIS (E, NE, DA) BLOCKS SYNTHESIS (5HT)

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

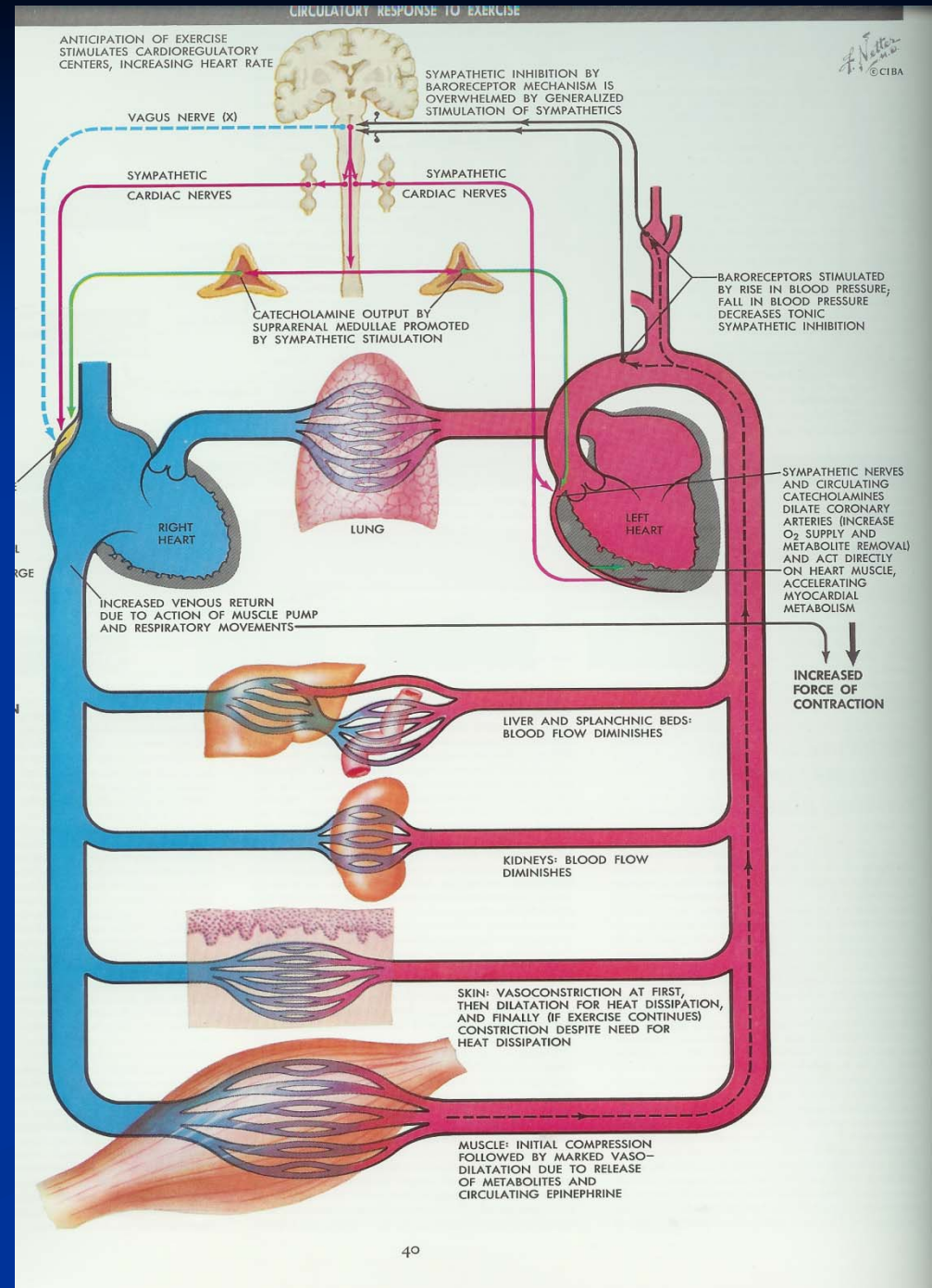
- Cocaine: formally used as local anesthetic
- Amphetamines and others: effective for attention deficit disorder (e.g. methylphenidate) and sometimes used for weight loss
- Potentially very toxic to CNS and heart
- May cause psychosis
- Intranasal use causes nose damage

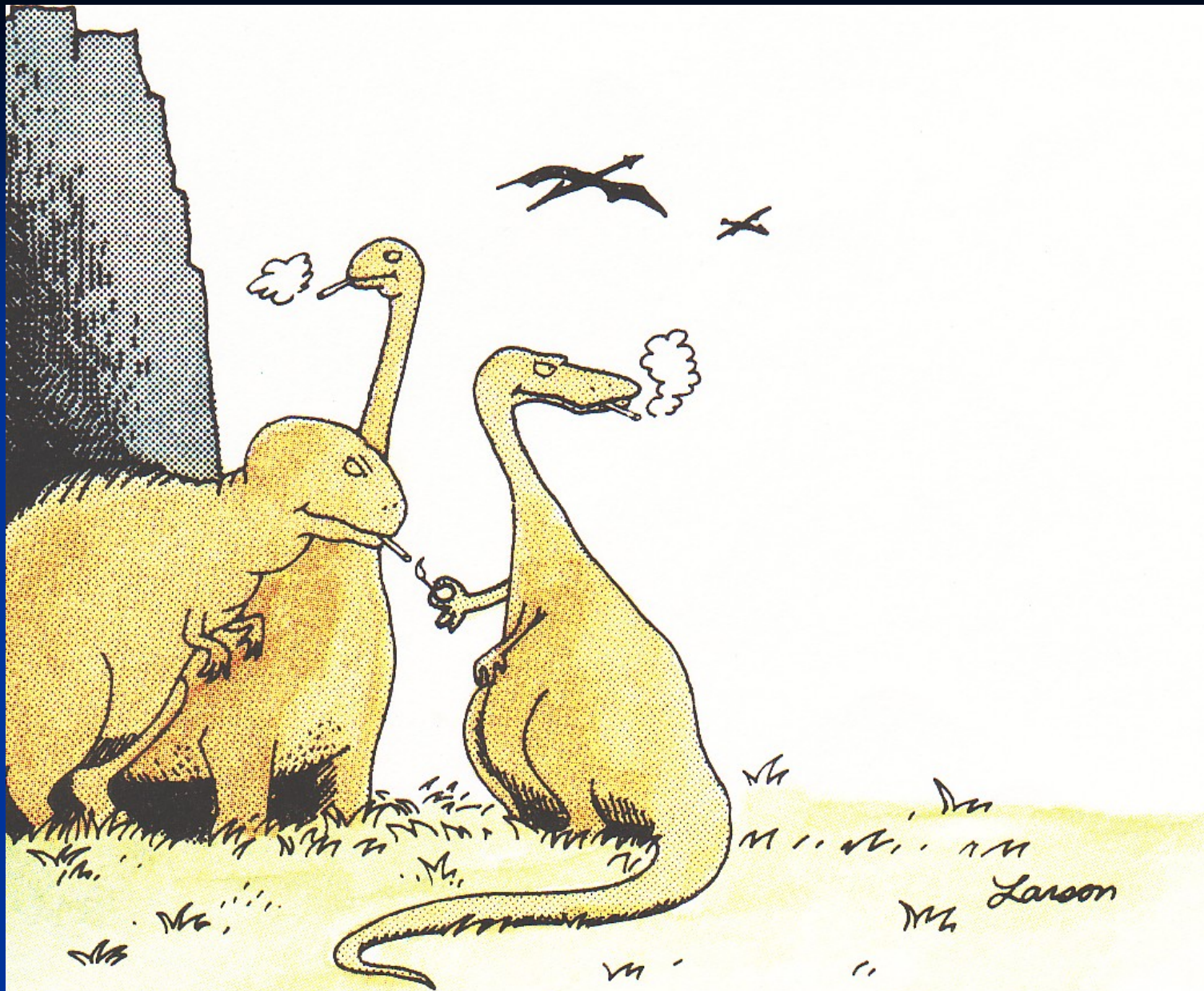
Pharmacokinetics of Drugs of Addiction

Drug delivery: process and systems

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

■ Circulation

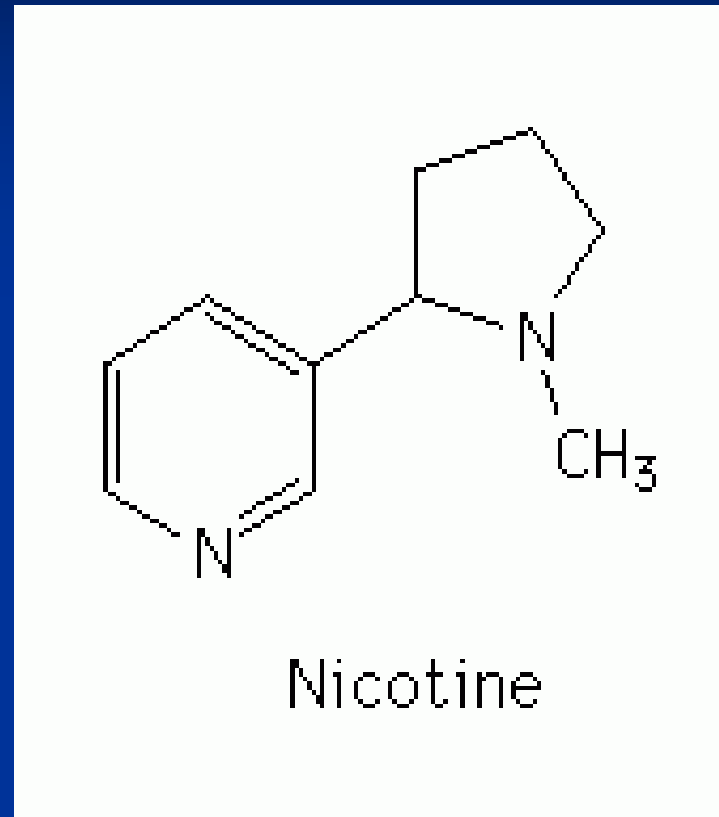




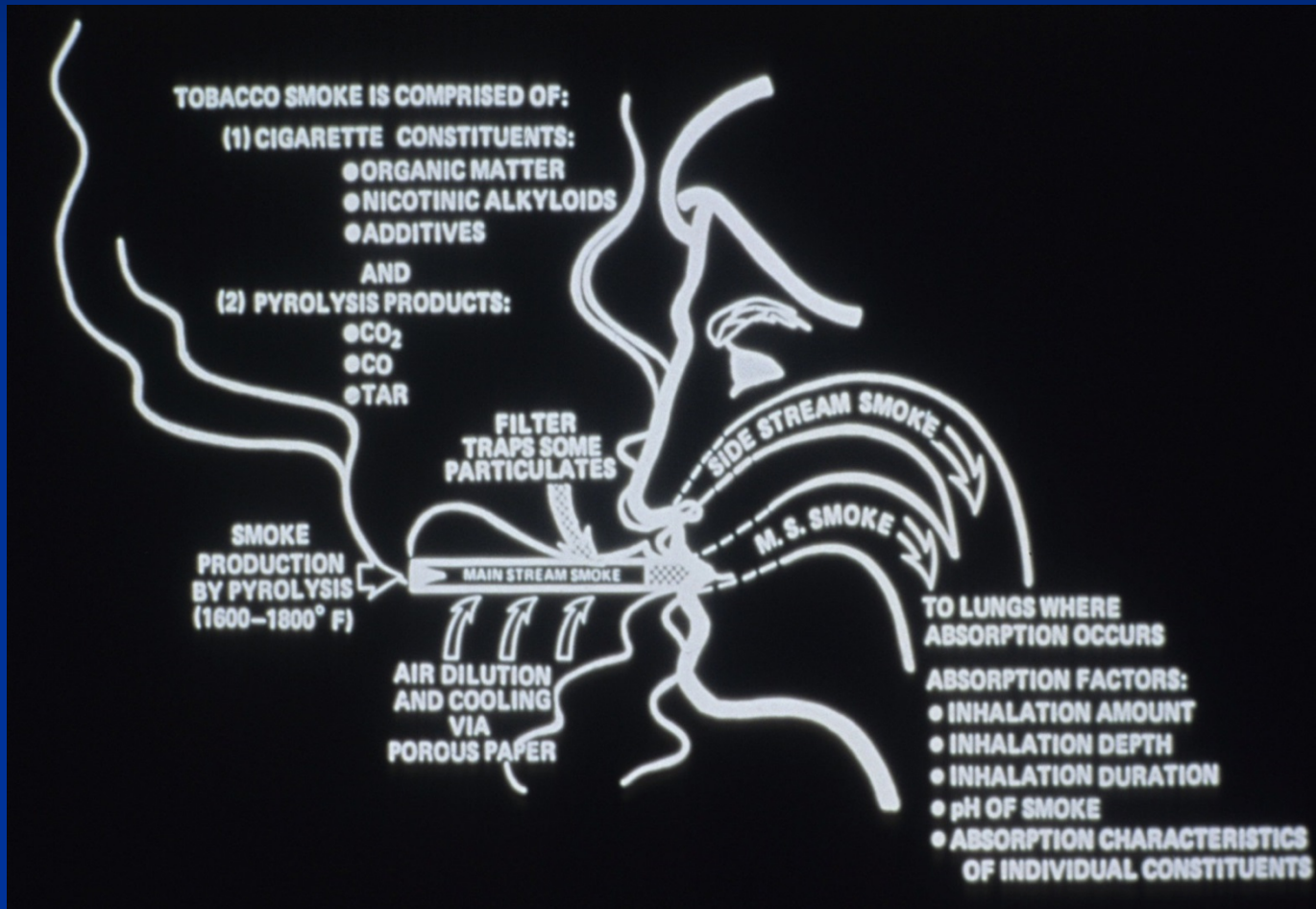
The real reason dinosaurs became extinct

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.



Absorption & Fate of Cigarette Smoke







Electronic Cigarettes (e-cigs)

- Device: mouthpiece and 2 interlocking plastic tubes. Distal tube is rechargeable battery. Proximal tube is a cartridge with heating element and liquid nicotine and propylene glycol or glycerol reservoir.
- Some cartridges have impurities including polycyclic aromatic hydrocarbons.
- Lipoid pneumonia from use has been reported.

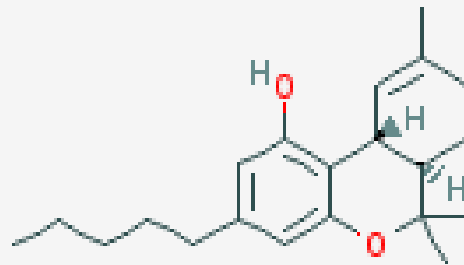
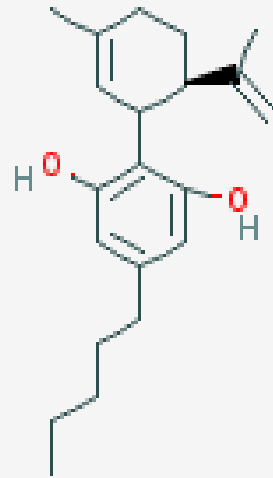
Marijuana/THC

- 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
- Cannabinoids vaporize at about 200 deg F

Endocannabinoids

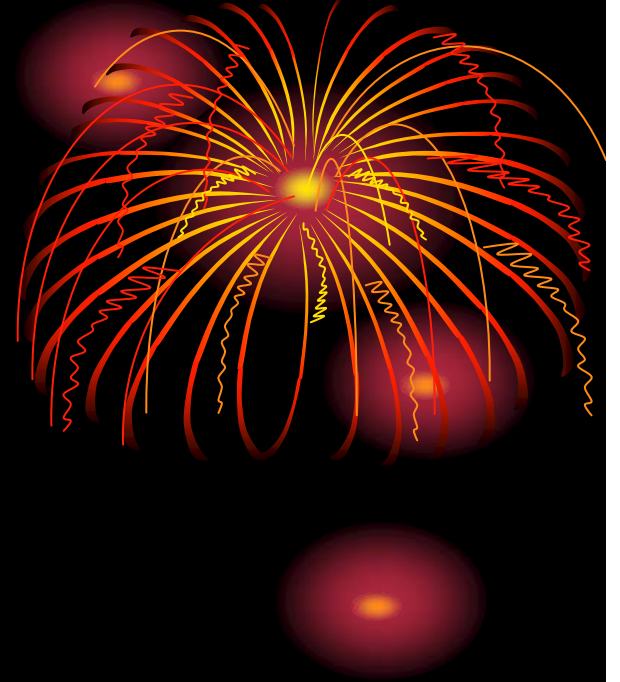
- Anandamide and 2-arachidonylglyceride (2AG)
- Cells release chemicals locally and interact with local cells (paracrine system)
- Action on CB-1 receptors leads to net anabolic action (i.e. net increase in energy intake and storage).
- Includes: Stimulates food intake, increases storage of fat, stimulates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

Cannabidiol and THC



Cannabidiol

- Major component of Marijuana
- Little effect on CB1 receptors
- Blocks breakdown of anandamide
- Does not lead to euphoria
- Appears to be useful for spasticity, seizures, and pain
- Approved in many countries and under study in USA



- 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>

Ally, now 27yo 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

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

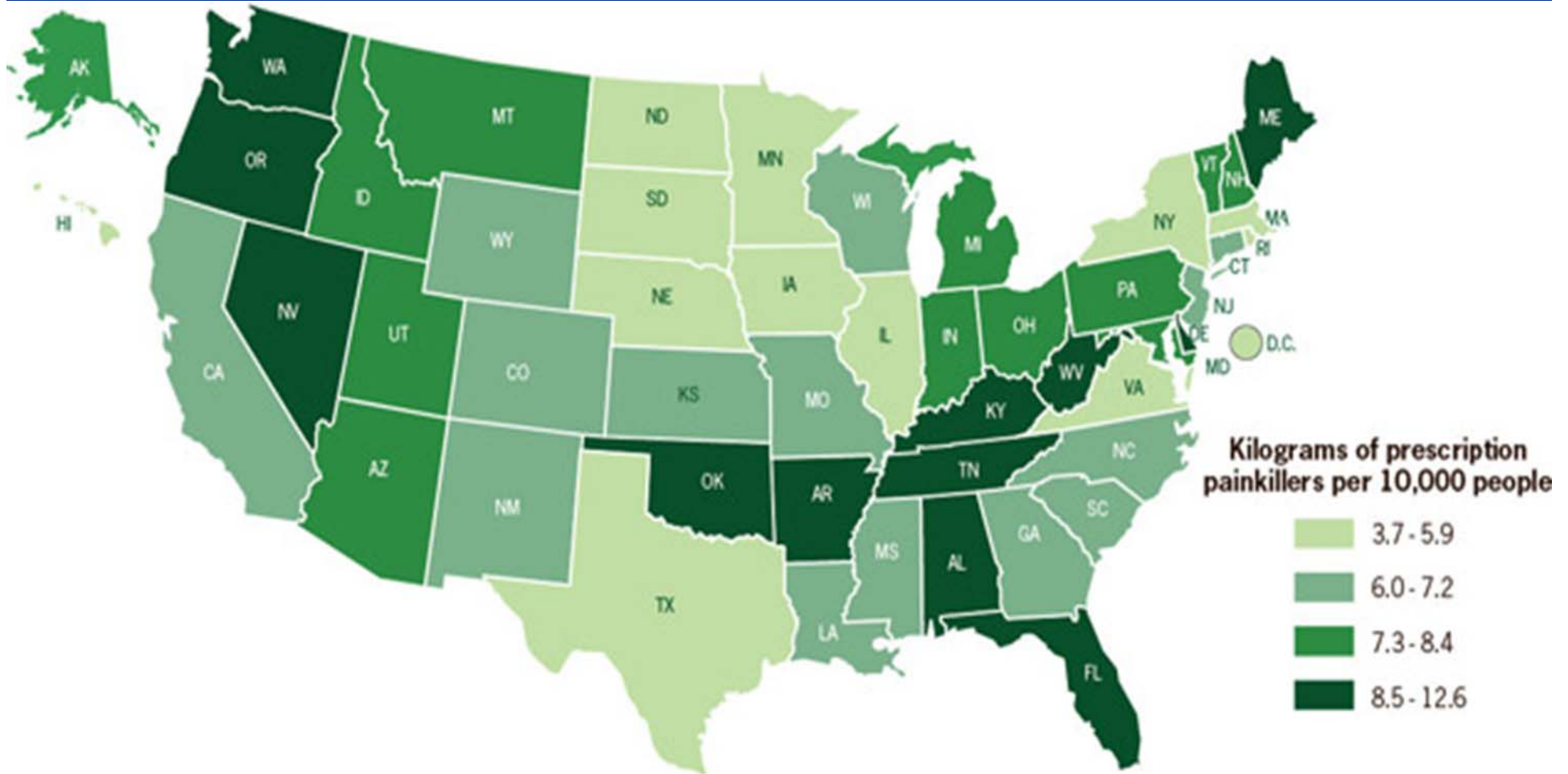
- Relapsed to high dose oral opioids
- 6/04, admitted to opioid agonist treatment program (IHC) using methadone
- Dose up to 80mg to help with anxiety as well as addiction
- Tapered down to 35mg over 3mo.
- 2/15/05, Suboxone induction done

Casey on buprenorphine

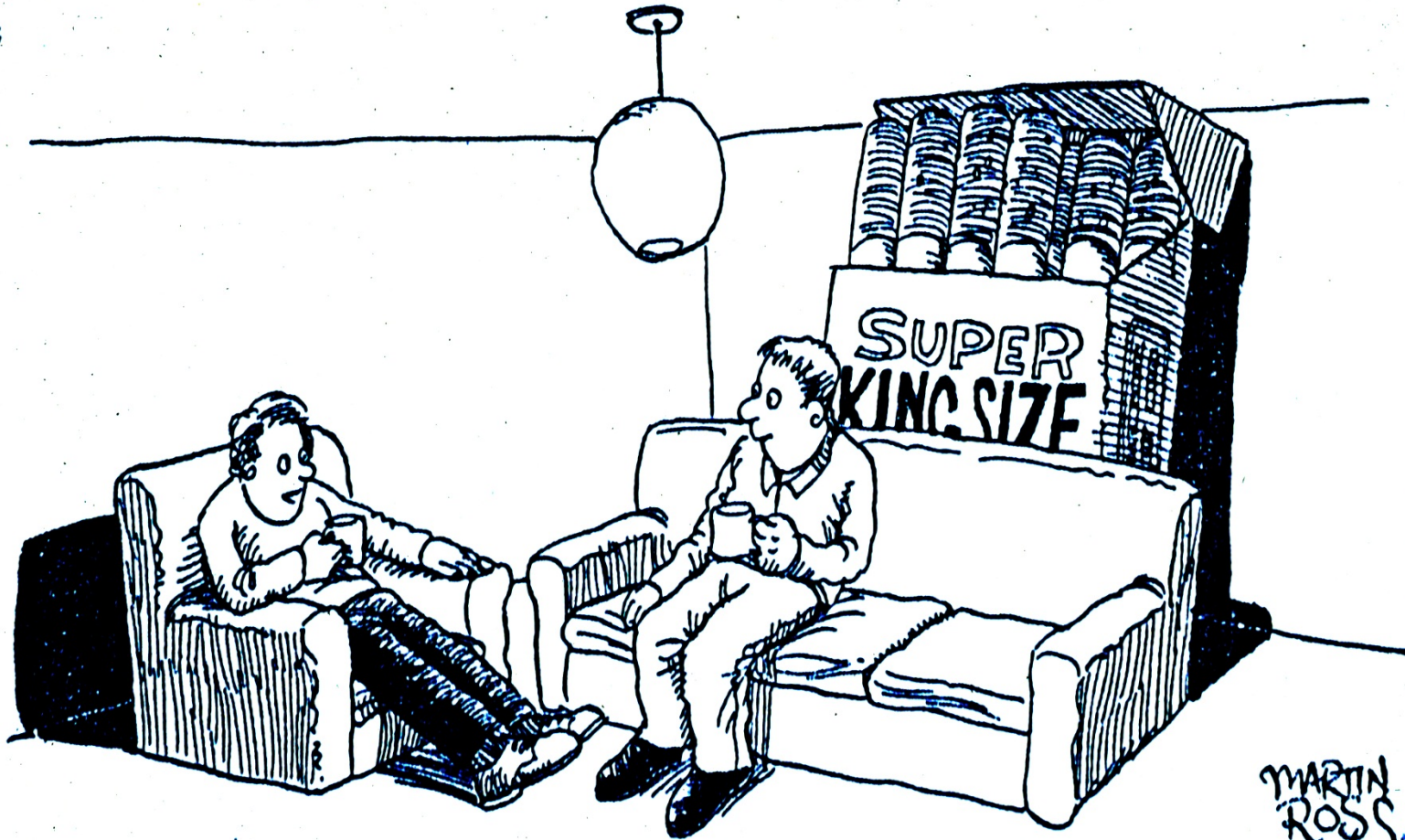
- 2/17/05, c/o diarrhea, cold, chills, rhinorrhea, antsy
- Dose increased up to 32mg over the next month
- 4/12/05, Feels “normal” and “got stabilized”
Says “grateful” for med
- Now on 16mg/d after slow taper. Feeling well and doing well with family and work.

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



© FUNGI



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