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—Retired 6/18**
- **Addiction Medicine: diagnosis, treatment and referral of drug dependent patients, treatment 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 current news
- Stimulate further inquiry and/or research into addiction medicine

Definition of Addiction (1/12, ASAM)

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

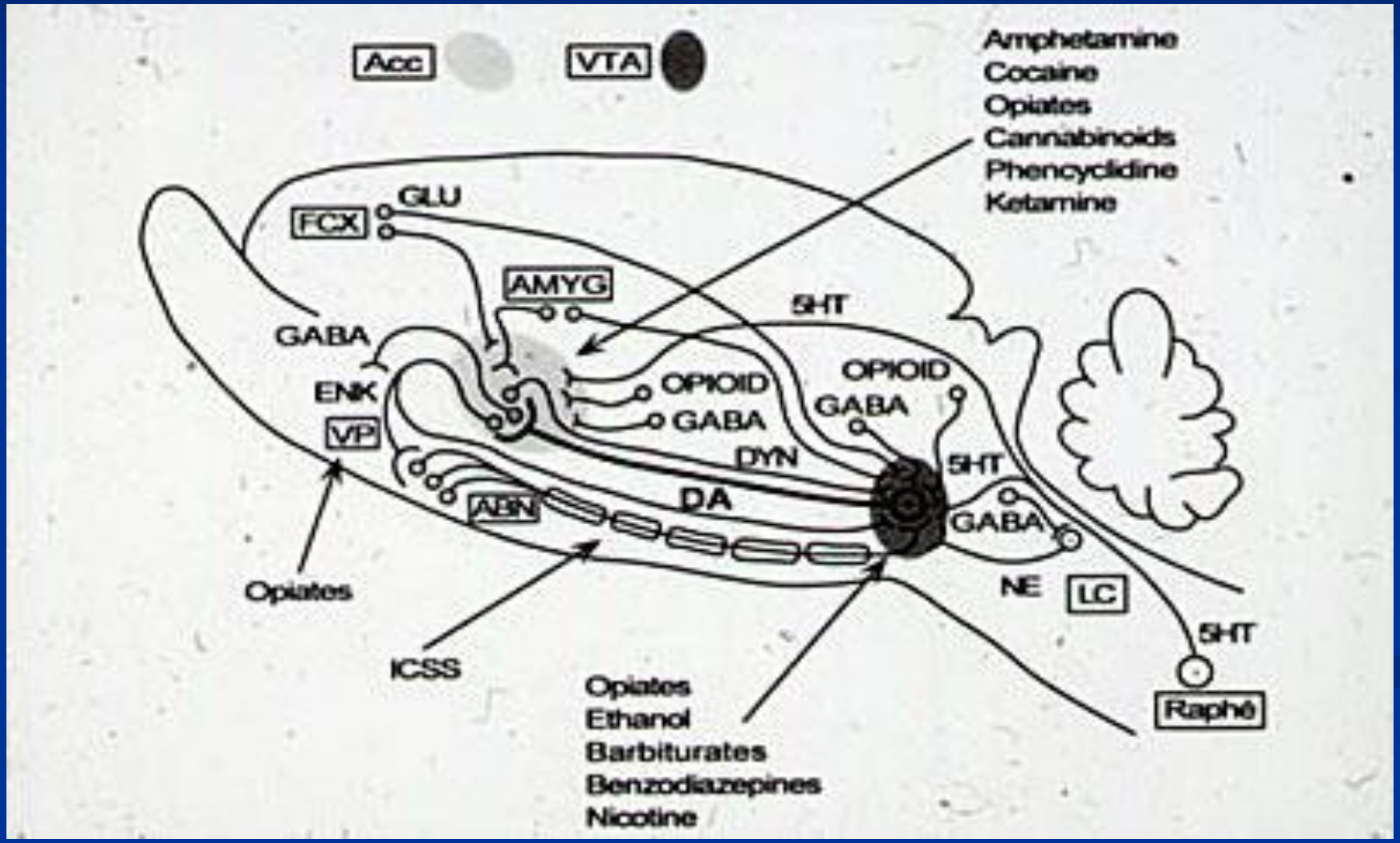
A disease characterized by continuous or periodic:

- 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

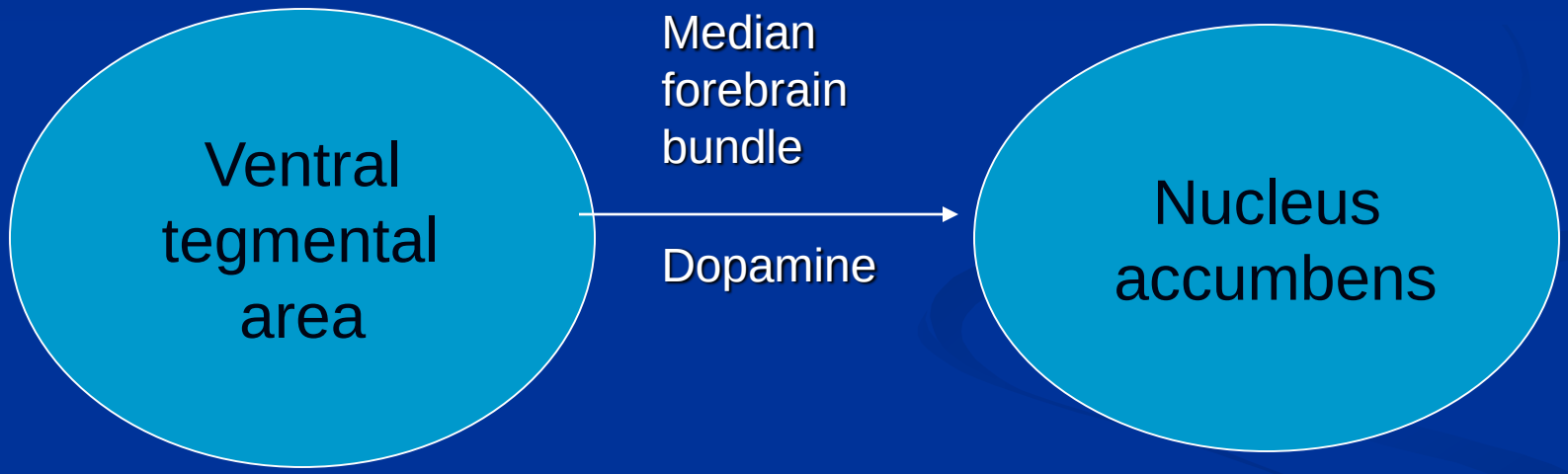
- Loss of control
- Craving and compulsion
- Continued use despite adverse consequences

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**: CH_3-CH_2OH
- **Absorption**: mostly intestines; also stomach and lungs
- **Metabolism**:

$CH_3CH_2OH + NAD^+$ (alcohol dehydrogenase) → $CH_3CHO + NADH + H^+$

$CH_3CHO + H_2O + CoA + NAD^+$ (aldehyde dehydrogenase/blocked by disulfiram) → CH_3COO-CoA (Acetyl CoA)$+ NADH + H^+$

Fluid Mosaic Model of Plasma Membrane Structure

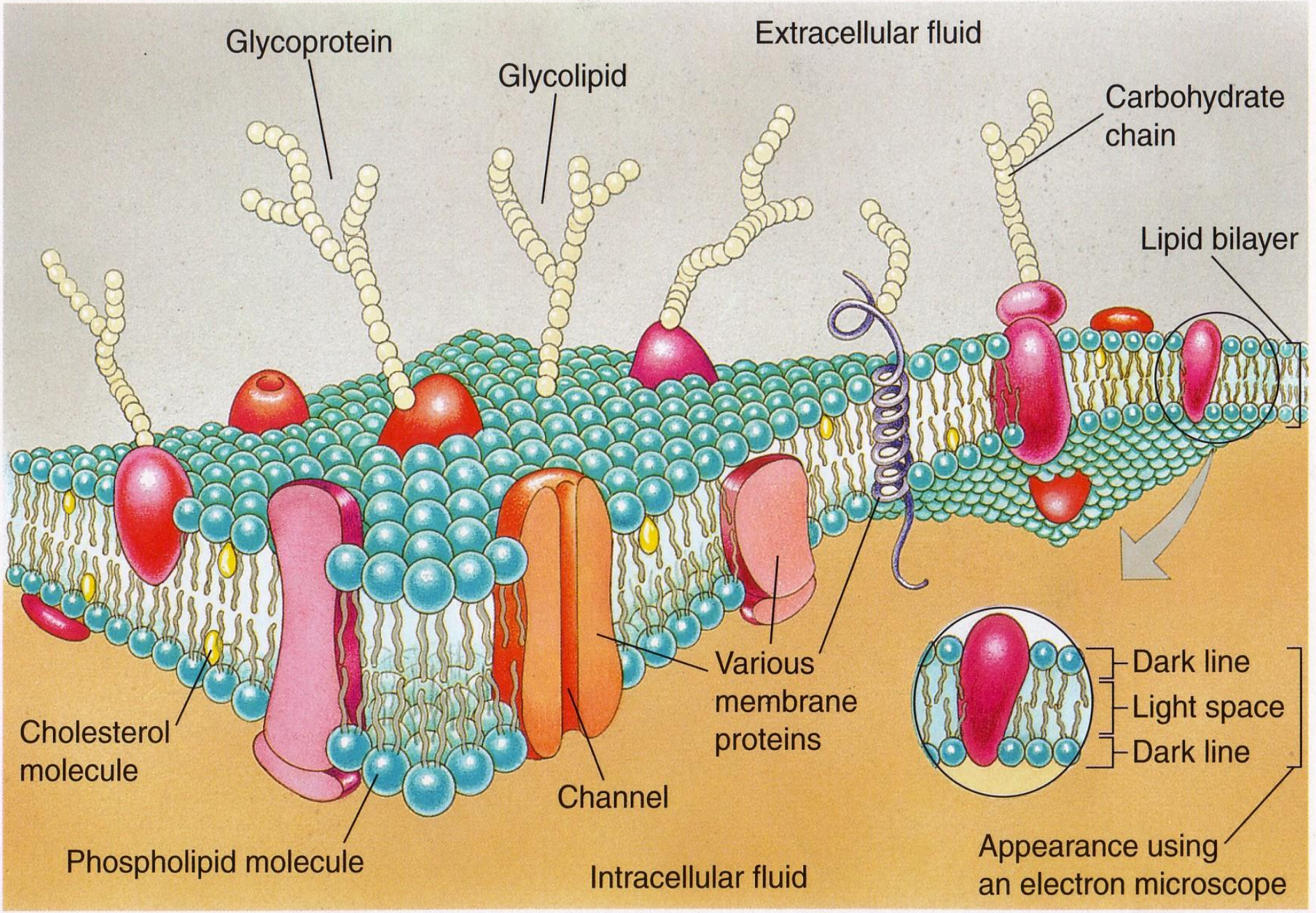
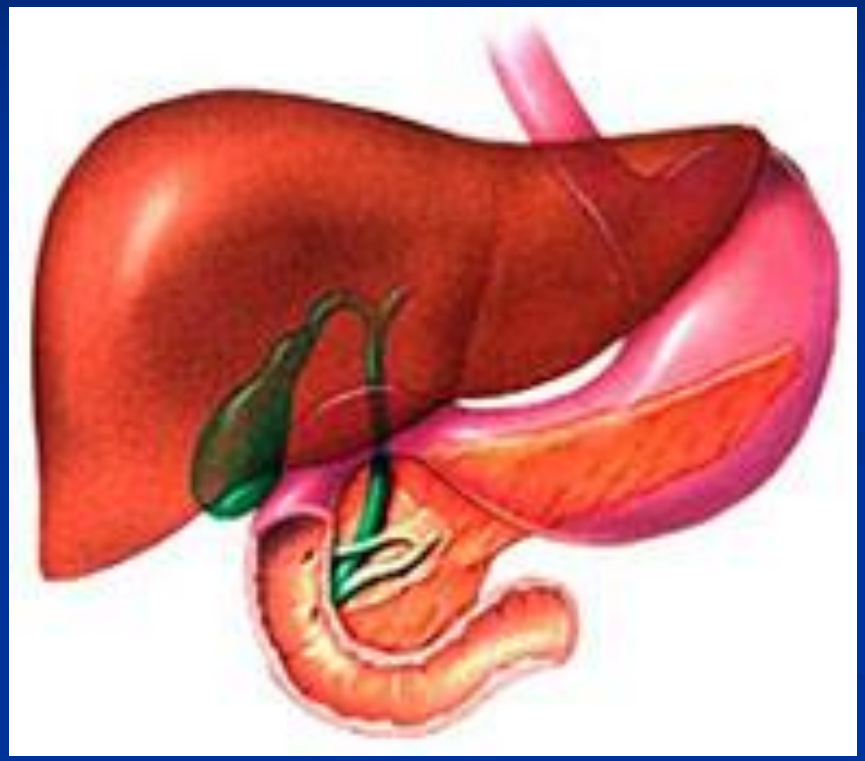


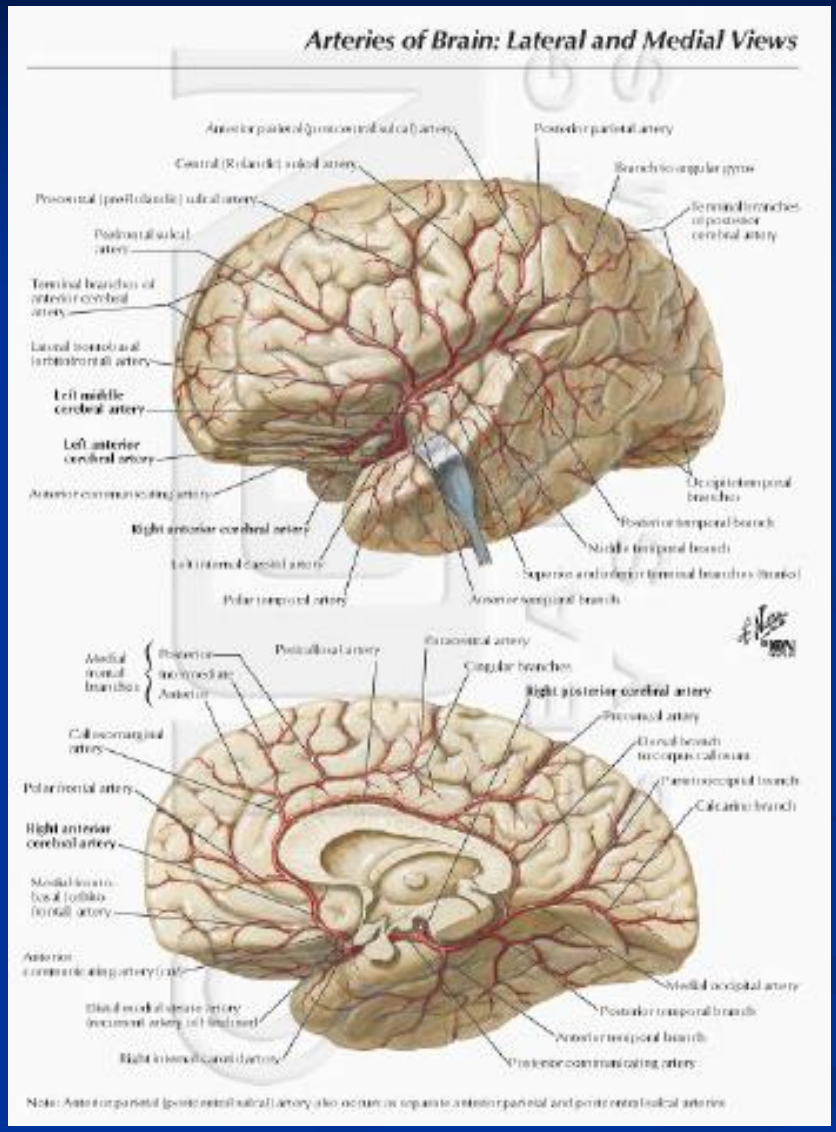
Table 1. Systemic Effects of Alcoholism

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

UGI Tract, liver, and pancreas

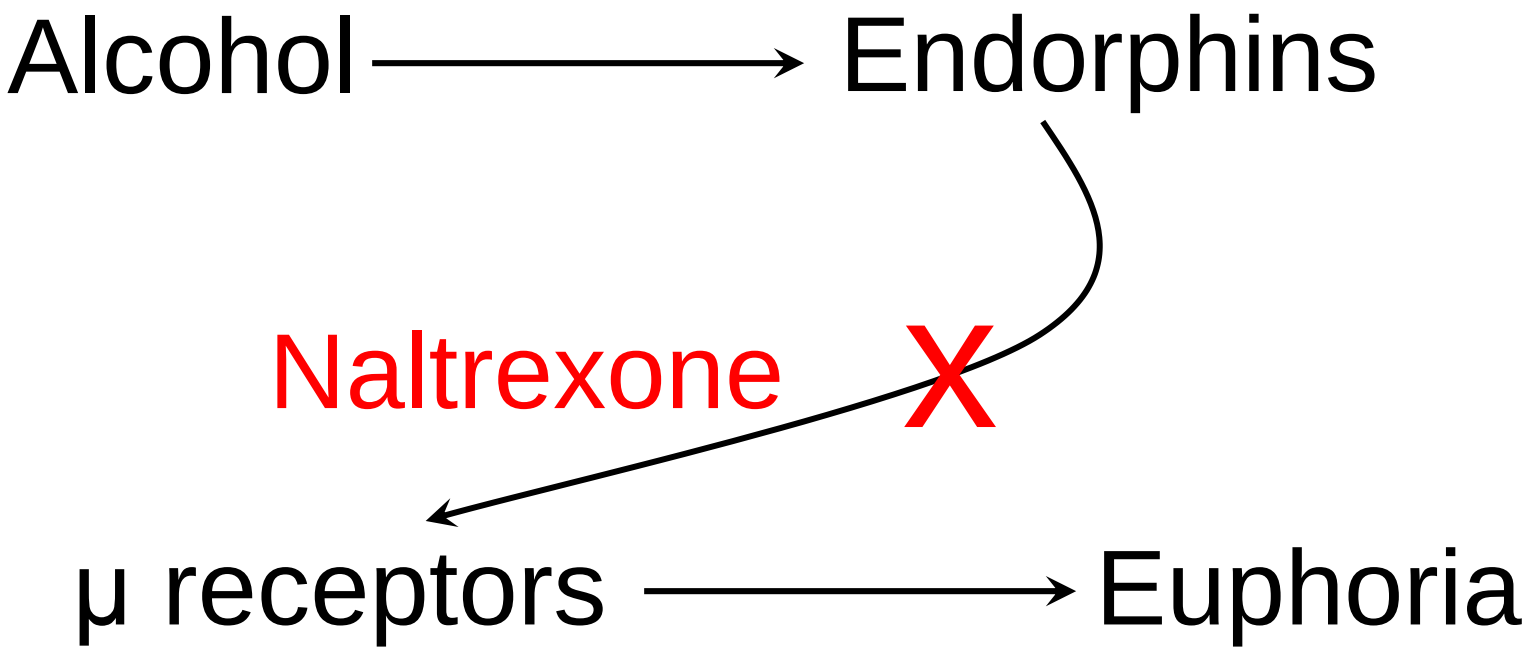


Brain


Arteries of Brain: Lateral and Medial Views
Left middle cerebral artery
Left anterior cerebral artery
Right anterior cerebral artery
Polar temporal artery
Anterior temporal branch
Middle temporal branch
Posterior temporal branch
Occipitotemporal branches
Posterior communicating artery
Right posterior cerebral artery
Precuneal artery
Parieto-occipital branch
Calcarine branch
Medial occipital artery
Posterior temporal branches
Anterior temporal branch
Polar frontal artery
Right anterior cerebral artery
Anterior communicating artery
Pericallosal artery
Callosomarginal artery
Medial frontal branches
Angular branches

Mechanism of action: Ethanol on the brain

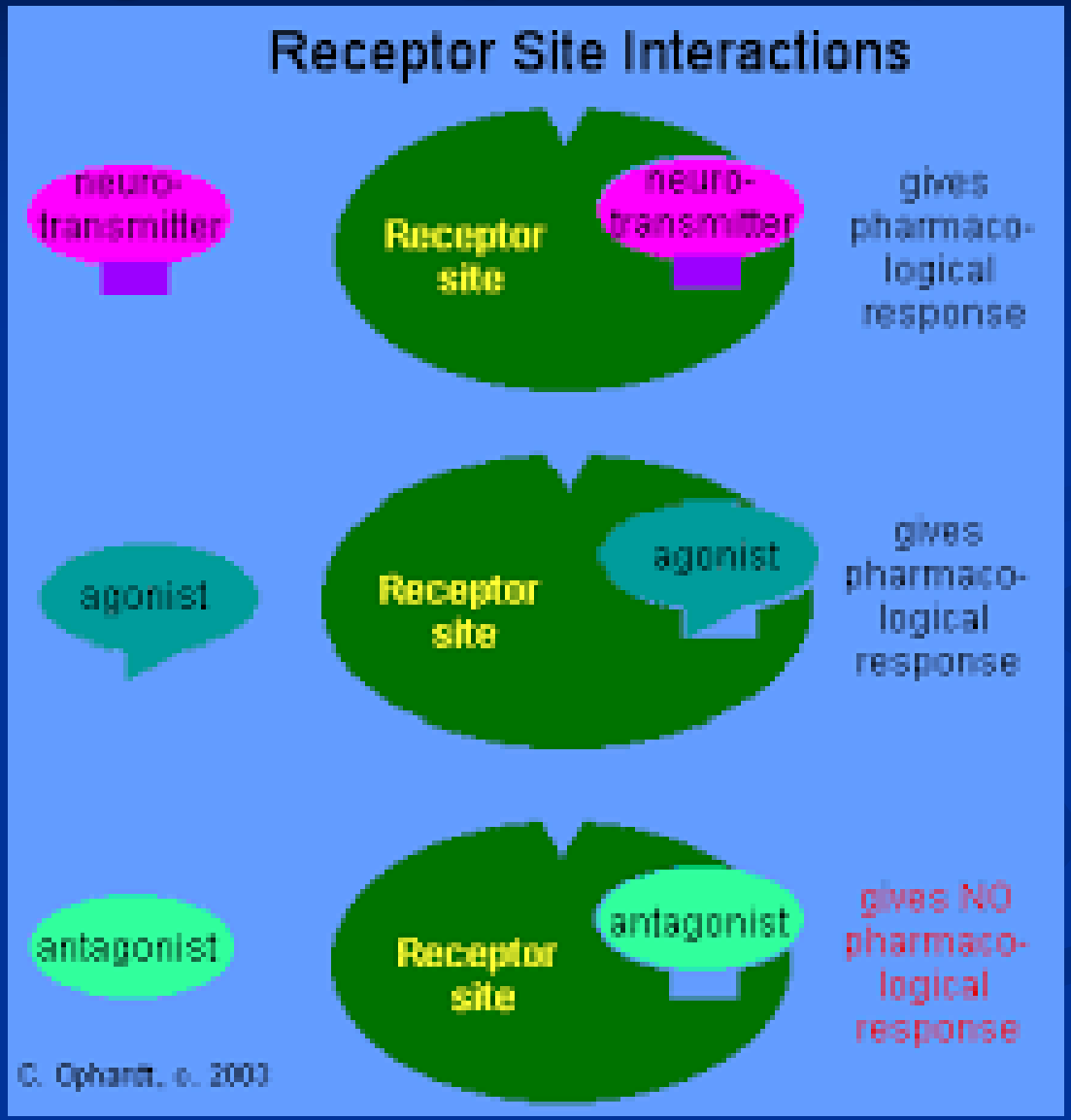
- Triggers release of endorphins
- Membrane effect
- Interacts with GABA and glutamate receptors


Alcohol
Endorphins
Naltrexone
X
μ receptors
Euphoria

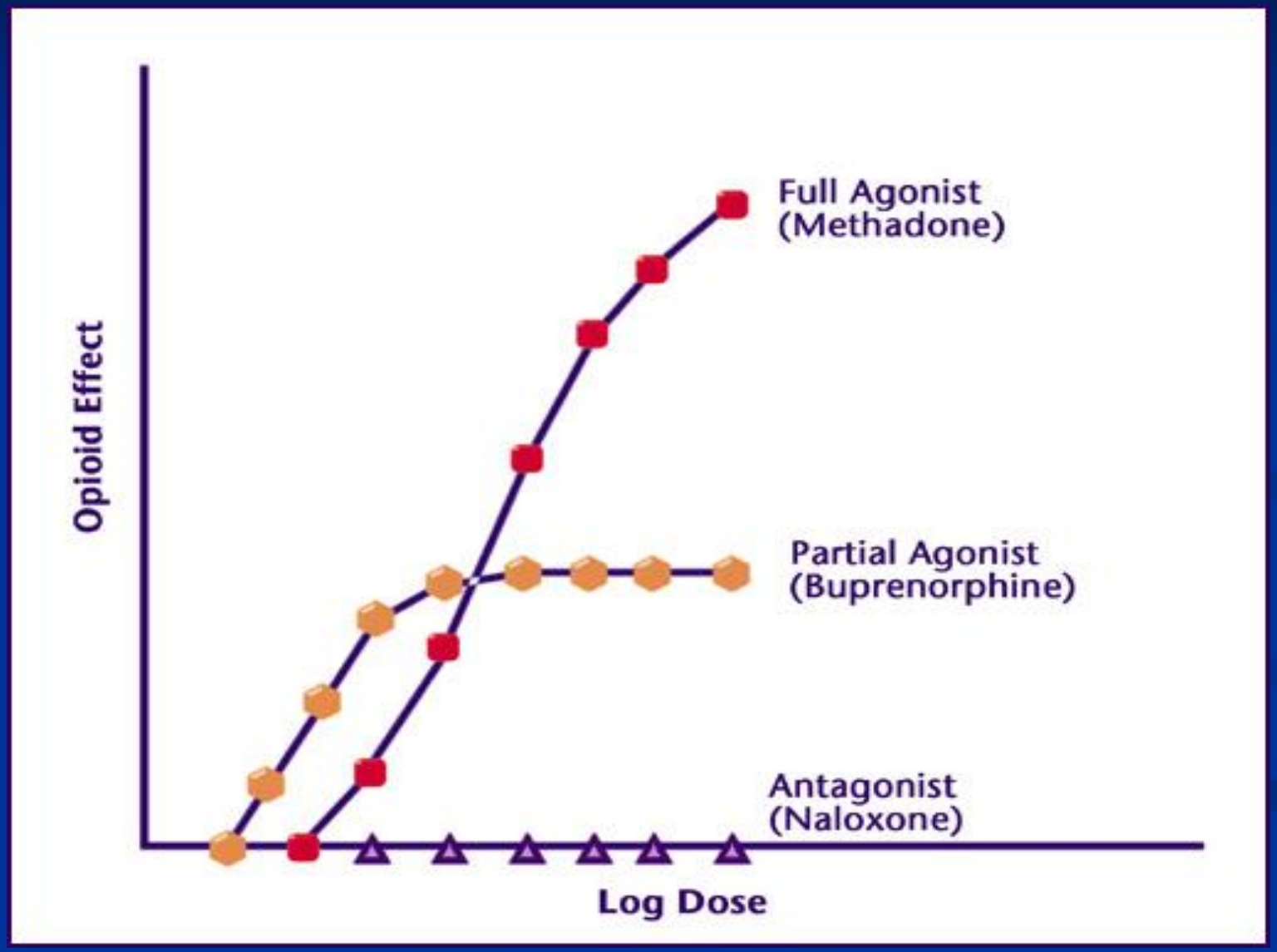
Pharmacodynamics: The study of drug action in the body (especially drug-receptor interaction)

- 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 on 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)

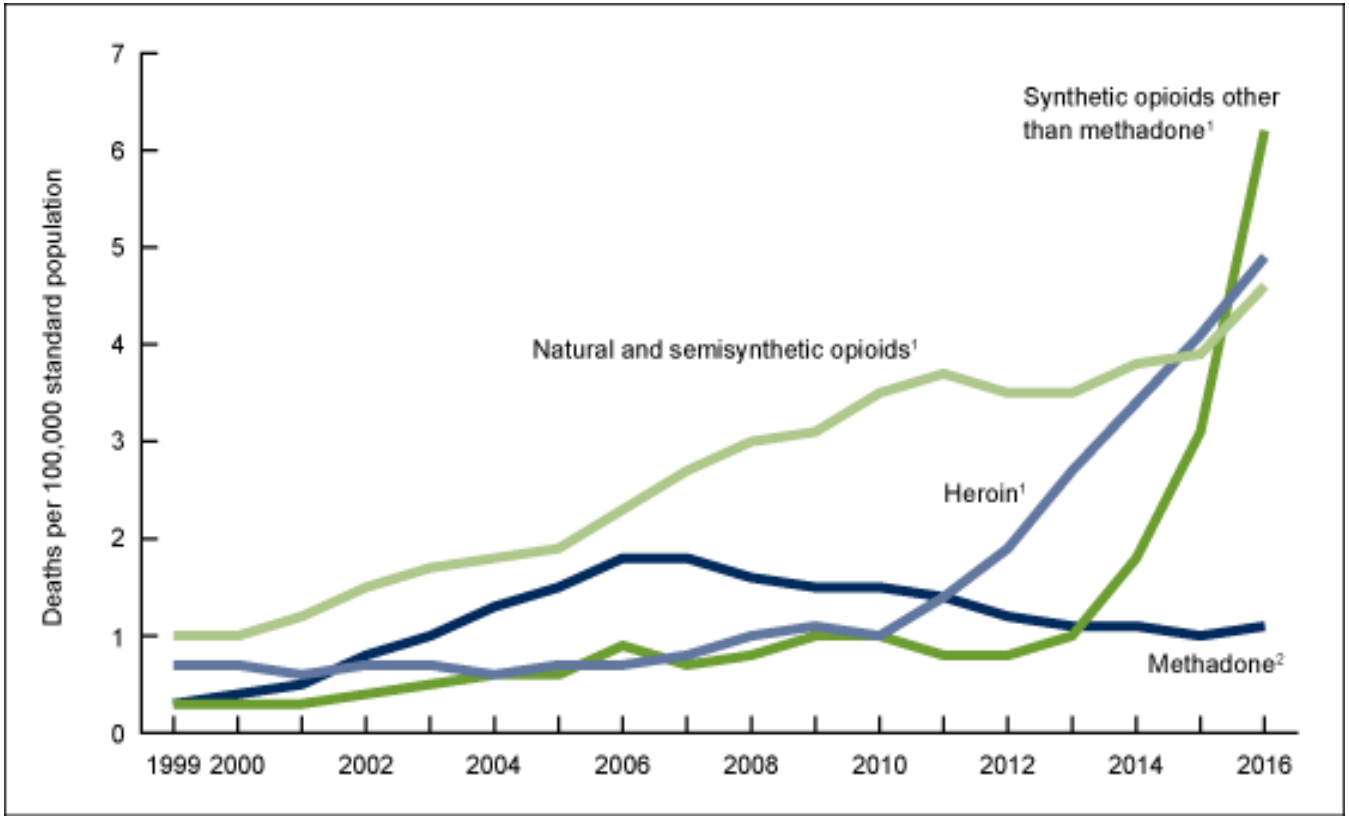
Opioids

- Very effective for analgesia.
- Major toxicity due to impurities; needle use with associated illnesses like HCV, HIV, and skin infections; and illegal behavior necessary to gain resources to purchase drug.
- Overdose leads to respiratory depression.
- In pure form very addictive but not especially toxic.

Hepatitis C

- Most common blood born infection in the USA
- An estimated 2.7-3.9 million people in the United States have chronic hepatitis C.
- Of every 100 persons infected with HCV, approximately:
  - 75–85 will go on to develop chronic infection
  - 60–70 will go on to develop chronic liver disease
  - 5–20 will go on to develop cirrhosis over a period of 20–30 years
  - 1–5 will die from the consequences of chronic infection (liver cancer or cirrhosis)
- HCV can be eradicated from the body—CURED!

Opioid OD Trends



+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.

SAMHSA
Substance Abuse and Mental Health Services Administration

Opioid Overdose

- 2014-- 47,000 drug overdose deaths in USA. 61% (28,670) involved an opioid (often fentanyl or derivative). This is more than 7 times the 4,000 people killed by these drugs in 1999.
- 78 people die each day in USA from an opioid related overdose.
- Naloxone can immediately reverse an overdose and can be delivered in the community.

Signs of Opioid Overdose

- Extreme sleepiness, inability to awaken verbally or upon sternal rub.
- Breathing problems that can range from slow to shallow breathing in a patient who cannot be awakened.
- Fingernails or lips turning blue/purple.
- Extremely small “pinpoint” pupils.
- Slow heartbeat and/or low blood pressure.

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

Buprenorphine Pharmacology

- Mean elimination half life of 37hrs
- Metabolized in liver mostly by CYP3A4
- 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 Bioavailability

- Good parenteral bioavailability
- Poor oral bioavailabilty
- Fair sublingual bioavailability—peak concentrations 30-60min post dose
- Combined with naloxone (Suboxone) which is very poorly absorbed sublingually to prevent diversion
- Considerable variability between patients in bioavailability of tablets

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

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 and opioid dependency

Recent ED case. SHUD, 12/1/18

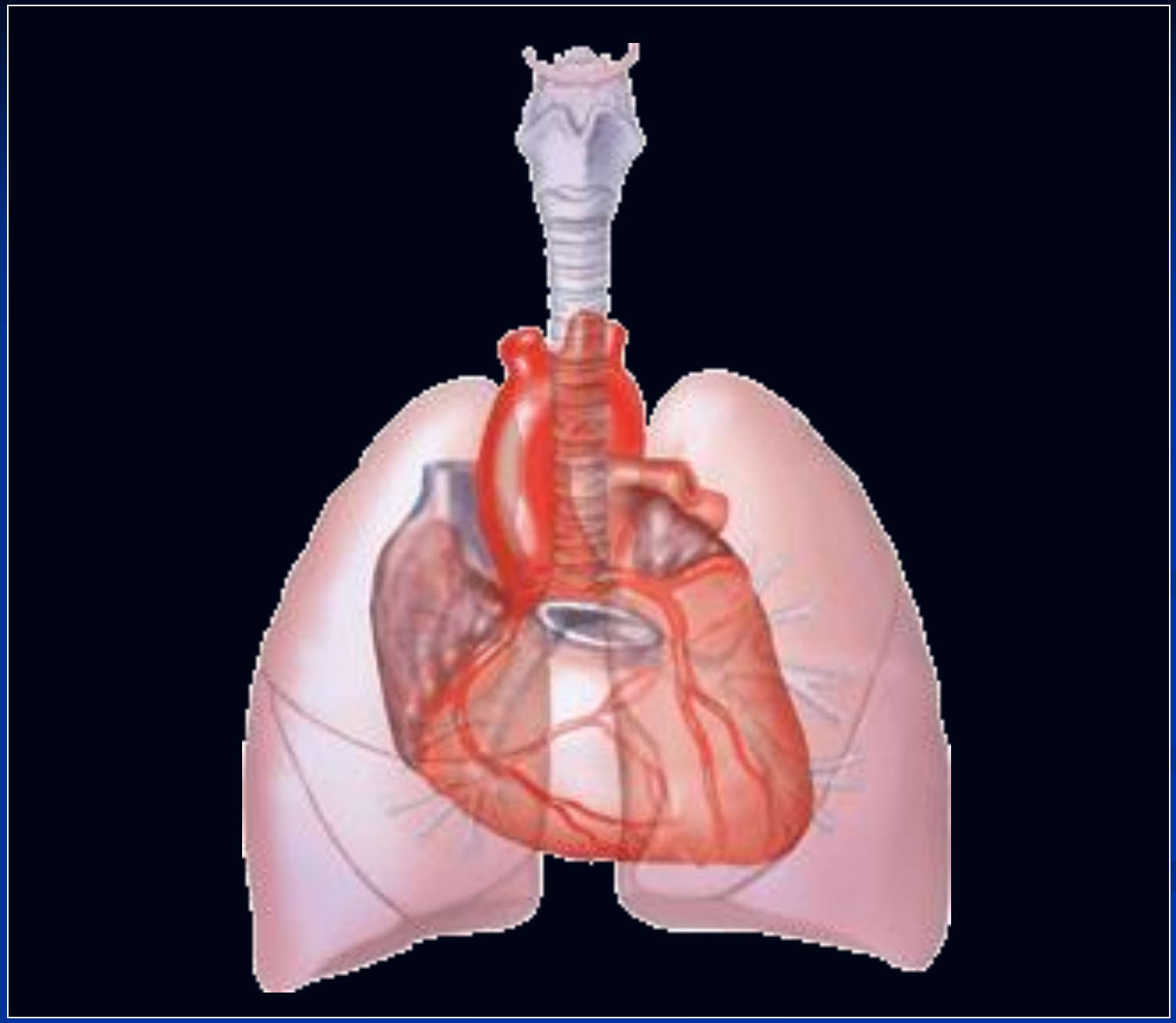
- KC, 37yo man
- Was at HWY 99 camp
- Found cyanotic. Reported had just used IV heroin. Reported previous use was 9d ago.
- Bystanders administered 2mg intranasal naloxone.
- CAHOOTS staff gave him another 2mg intranasal naloxone and 2mg IM in route to ED.
- PMHx: BPD, untreated, and HTN. Current smoker. 3 prior SHED admits this yr for OD.
- PE: BP: 155/105, P: 99, R: 16, BMI: 25. No mention of pupil size. He was diaphoretic. Otherwise exam normal.

Recent ED case. SHUD, 12/1/18
continued

- Given 1l Normal saline, buprenorphine 2mg, and ondansetron
- 3 hrs later was resting comfortably. Given another 2mg buprenorphine.
- Expressed interest in stopping heroin.
- He was informed about what happened.
- ED doc referred him for ongoing buprenorphine therapy.

Vision to Assist with Addressing the Opioid OD problem

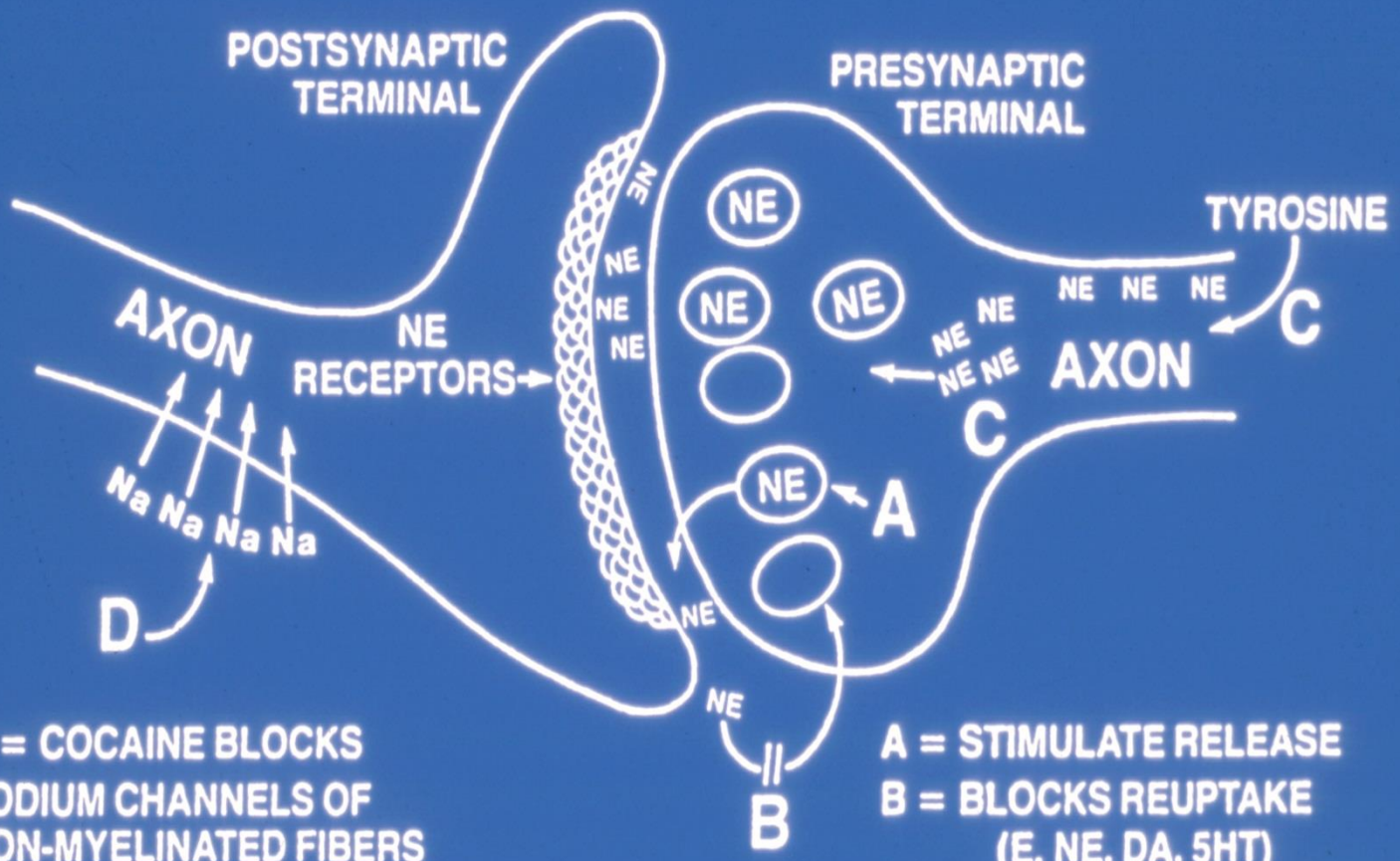
- Situation: Accidental opioid OD reversed with naloxone. Patient wakes in opioid withdrawal. Many patients want to leave and deal with their withdrawal by getting another dose of opioid.
- Diagnosis: Opioid dependency with opioid withdrawal.
- Treatment for w/d: Buprenorphine is drug of choice for opioid withdrawal.
- Treatment for opioid dependency: Opioid agonist with methadone or buprenorphine.
- Proposal: Begin treatment for opioid dependency in ED.
- Rx: 3d of Suboxone—dispensed from ED.
- Referral to buprenorphine prescriber. System to be established.



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

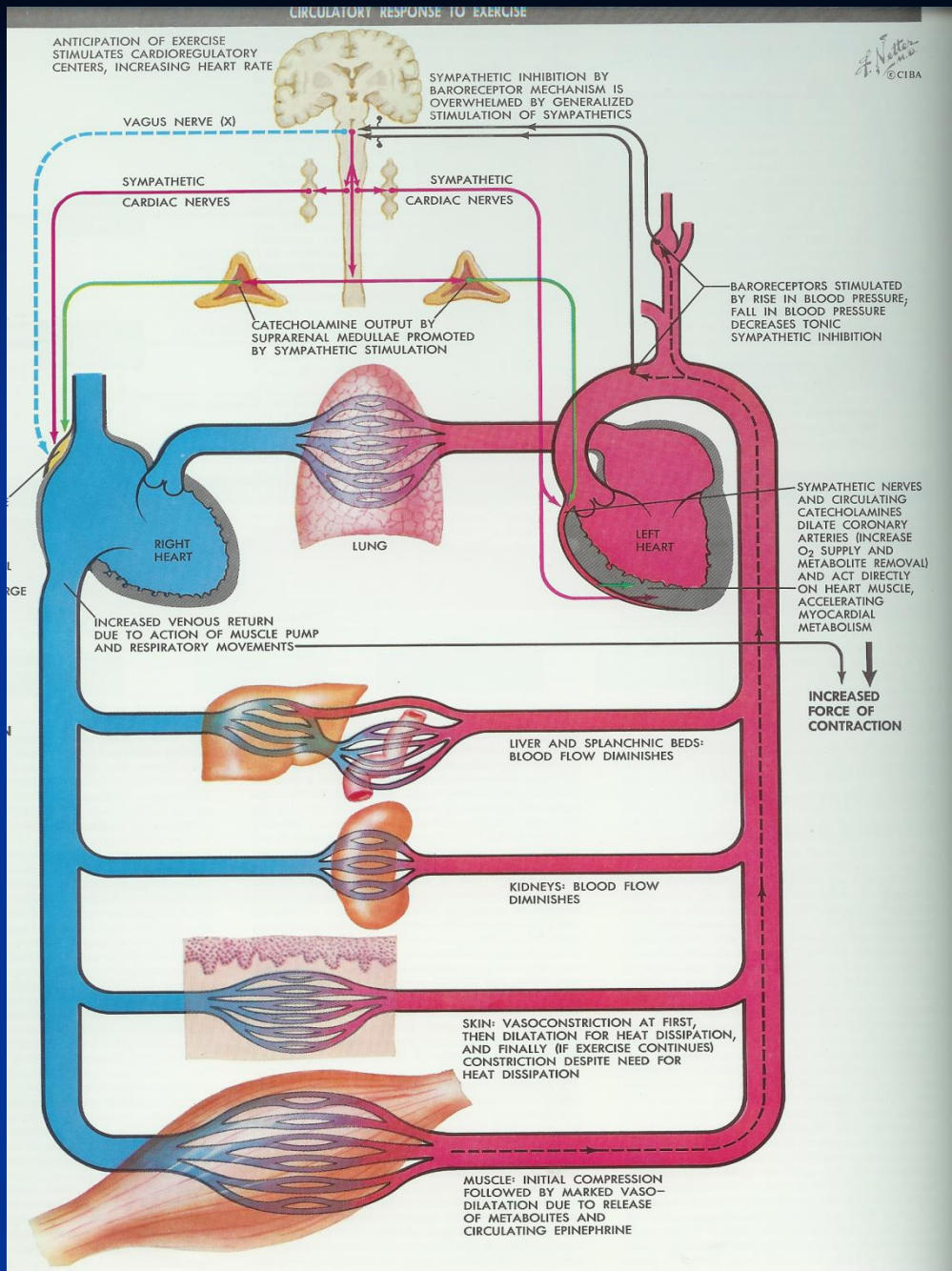
Stimulants: cocaine, amphetamines, and others

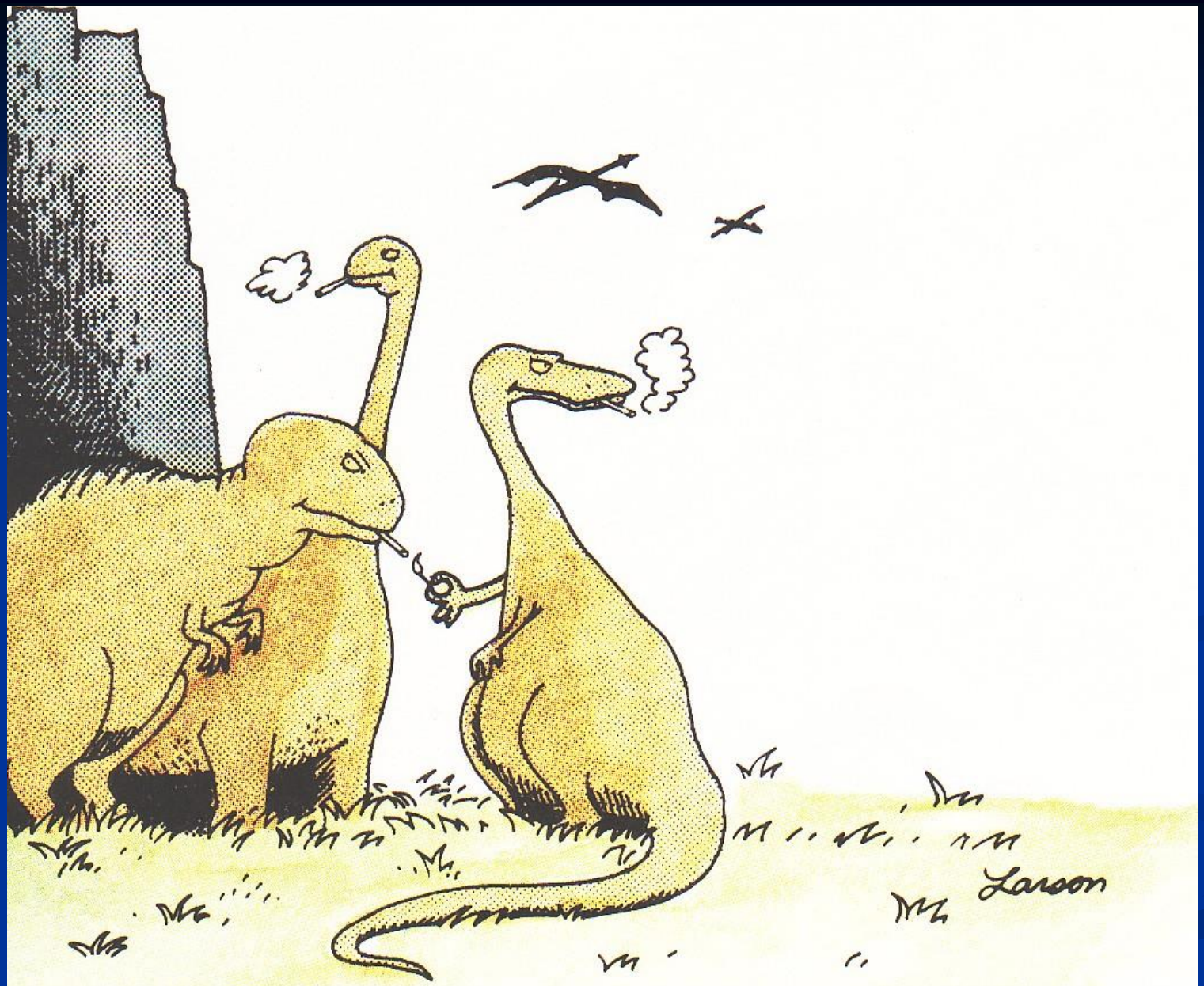
- Cocaine: formally used as local anesthetic
- Amphetamines and others: effective for attention deficit disorder (e.g. methylphenidate) and sometimes used for weight loss
- Potentially very toxic to CNS and heart
- May cause psychosis
- Intranasal use causes nose damage

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

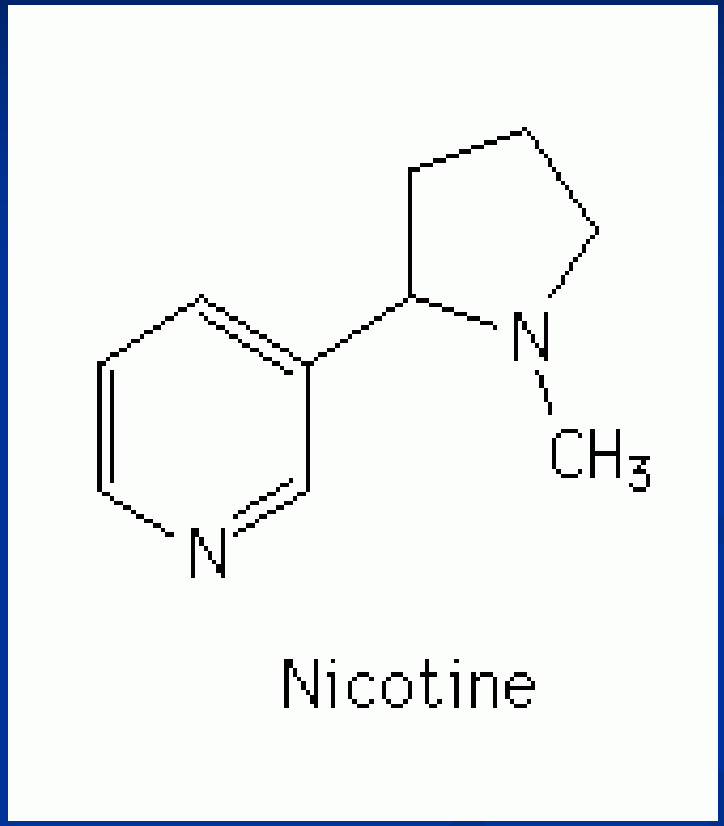




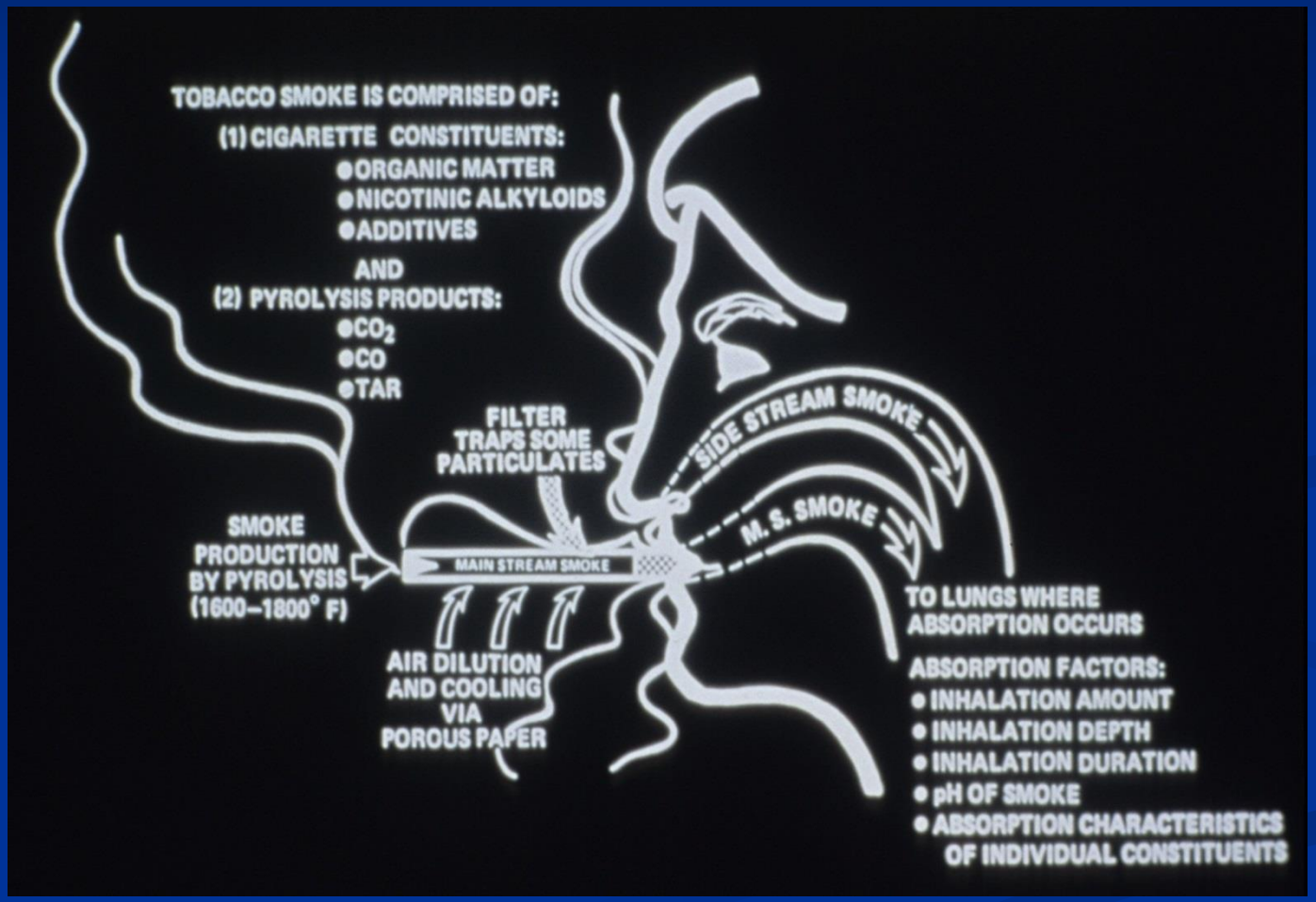
The real reason dinosaurs became extinct

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 rechargable 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.

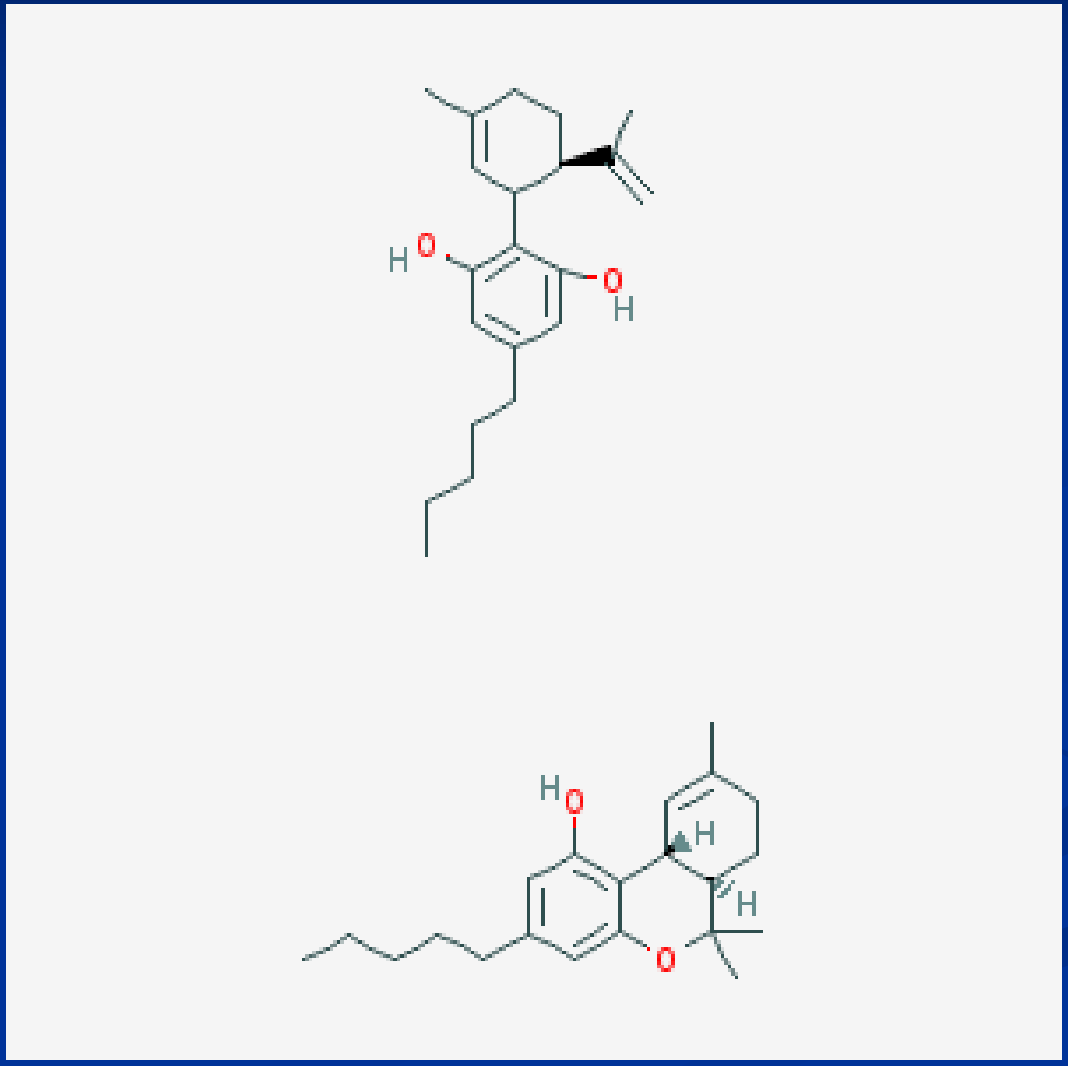
Endocannabinoids

- Anandamide and
  2-archadonylglyceride (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.

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, seizures, and pain. Maybe useful for cancer.
- Cannabinoids vaporize at about 200 deg F

Cannabidiol and THC



Cannabidiol (CBD)

- Major component of Marijuana
- Partial antagonist at CB1 receptors
- Blocks breakdown of anandamide
- Does not lead to euphoria
- Appears to be useful for spasticity, seizures, and pain and perhaps cancer.
- Approved in many countries and under study in USA

NATIONAL ACADAMIES OF SCIENCES, ENGINEERING, AND MEDICINE 2017 RESEARCH GAP RECOMMENDATIONS

- Increase funding
- Improve public health surveillance systems
- Address barriers to research.

- QUESTIONS