# Weight Loss Medications – Past and Present

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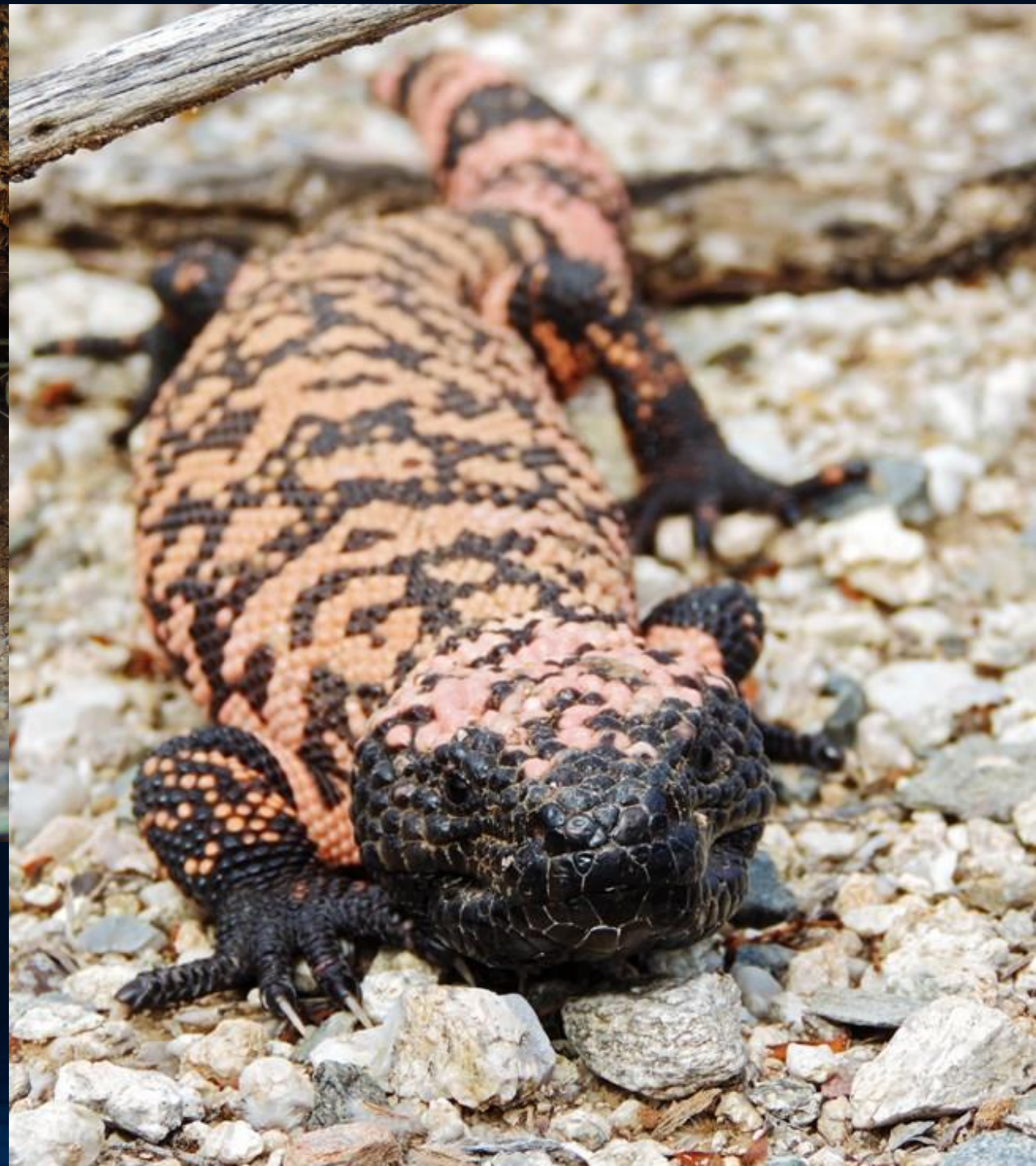
# Disclosures

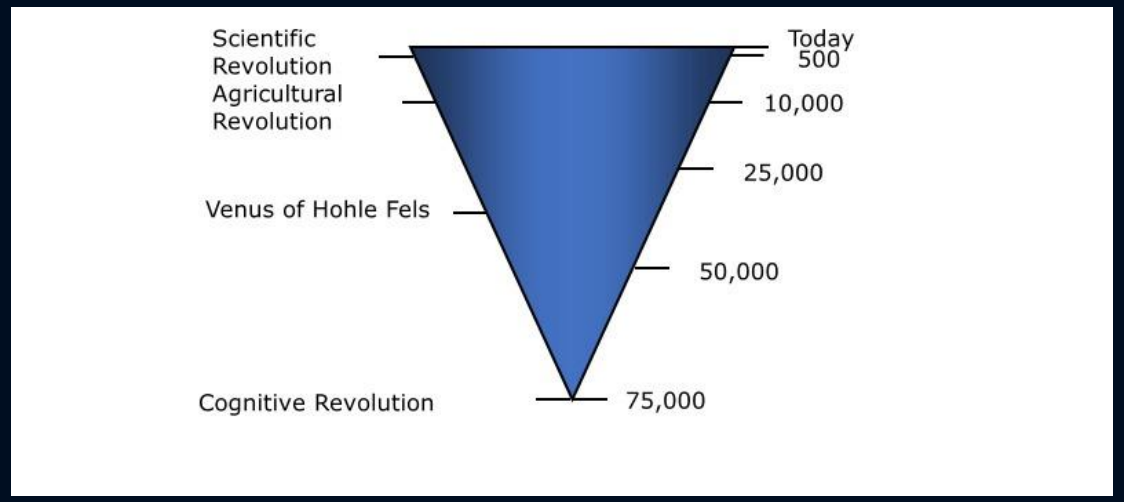
- None



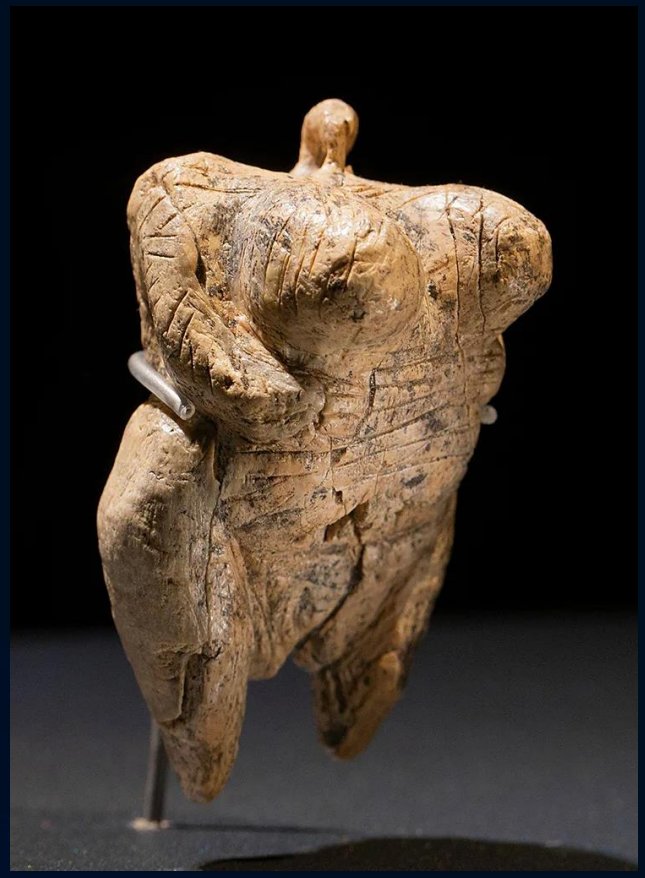
# Obesity - History

- Present since pre-history.
- From 2 million years ago until 10,000 years ago, multiple human species roamed the earth together.
- Humans species middle of the food chain until 400,000 years ago.
- Homo sapiens 300,000 years ago.
- We become the top of the food chain 100,000 years ago.
- Most animals at the top of the food chain made it there over millions of years. Humans jumped to the top rapidly.
- Food chain wasn't ready and neither were we. Perhaps are anxious and stressed because we aren't used to being at the top.

# Obesity - History




- Humans of 30,000 years ago had the same physical, emotional, and intellectual capabilities that we have today.
- Three milestones in human history. Obesity present nearly at cognitive revolution
- Today, nearly 70% of adults in the US are either overweight or obese.
- US obesity rates have tripled over the last 60 years.



# Obesity

- Lifestyle modification is first line
- Pharmacotherapy AND lifestyle modification
  - BMI ≥30 or ≥27 kg/m2 and at least one weight-related comorbidity, such as DM, HTN, hyperlipidemia, or CVD.
- Definition of success
  - Weight loss of 5% or greater after 12 months of treatment

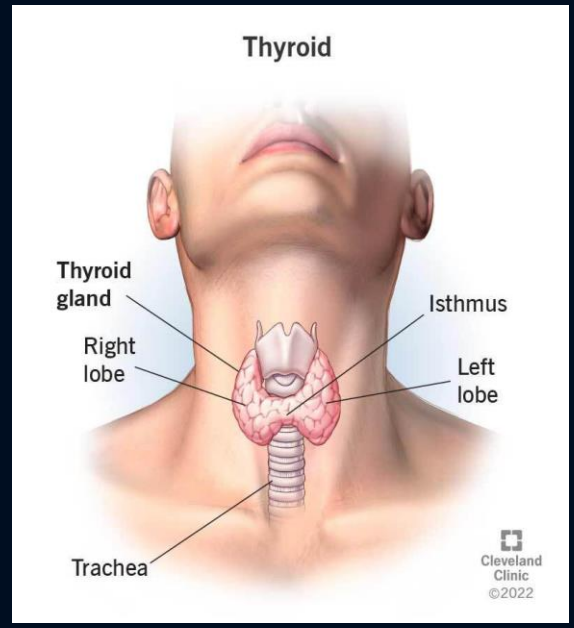
# Pre - Scientific Revolution (pre 1540 CE)

- Diet and exercise advised for 2500 years. Hippocrates
- Many descriptions of obesity in Greco roman texts
- Romans – diuretics, emetics and laxatives
  - The obese "should vomit in the middle of the day"
  - Emperor Vitellius

# Scientific Revolution 1540 – 1800

- Tobacco becomes a treatment
- Several textbooks published
- Diuretics, emetics, soap.
- A variety of theories about environment, humors, etc.

# Modern Era beings
# Thyroid Hormone 1893 – 1990's




- 1893 – Discovered hypothyroidism
  - Slowed metabolic rate with weight gain, slowed thought and speech.
  - Treatment with thyroid extract the process reverses
  - Thyroid and metabolism. Cause and effect – genie is out of the bottle
- Early 1900's – Iodine in patent medications
  - Allan's Anti-Fat; Frank J Kellogg's Safe Fat Reducer; Dr. Bertha C. Day's Fort Wayne prescriptions, Marmola, Newman's Obesity Cure, Chichester's Corpus Lean, Rengo, Dr. Gordon's Elegant Pill, Corpulin, Elimiton, Phy-th-rin, San-Gri-Na Trilene tablets

# Thyroid Hormone 1893 – 1990's

- Increases metabolic rate
- Safety concerns
  - Poor sleep, arrhythmia, heart failure, catabolism of protein--loss of muscle>fat
- Probably not effective unless caloric restriction

# Dinitrophenol: 1918-1938

- First, as an explosive during World War I
- French factory workers preparing in munitions factories during World War I lost weight.
- Uncoupling of ox-phos – Short circuit. Boosts metabolism over 50%
- Weight loss of 1.5 lbs per week. Most lost weight.
- Cataracts, lose eye site, neuropathy, hyperthermia and death. At therapeutic doses.
- Food, Drug, and Cosmetic Act of 1938 gave the FDA had the authority to act against drugs like dinitrophenol.

# Dinitrophenol: 1980-

- Texas physician began to make industrial DNP into tablets.
- Marketed as “Mitcal” for weight loss.
- Treated 14000 patients. Many side effects, one fatality.
- Convicted in 1984.
- Keep using DNP for medicinal purposes. Jailed for fraud in 2008.
- DNP still available on internet, primarily bodybuilders, weight loss
- Huntington’s disease

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# ‘Slimming pill’ drug to be classified as poison after at least 33 deaths

DNP is banned for human consumption but it has been advertised online as something that aids weight loss

Lucy Skoulding • Monday 30 January 2023 11:51 GMT • 12 Comments

Daily Mail

60p

Pizzas. Nachos. Rice pud...

2 DAY SUMMER DIET recipes your family will love

£150 OFF AT Boots

MORE GREAT OFFERS INSIDE

Coroner attacks online dealers who target the vulnerable

# BANNED SLIMMING DRUG KILLS MEDICAL STUDENT

Sarah Houston: Her body was found by a student friend

She was a healthy medical student whose parents, brother and sister were all doctors.

But ... obsessed with her weight ... Sarah Houston, 25, was secretly taking a banned and dangerous slimming pill.

By Chris Brooke

Around when she took her perpetrator her illness was finally under control, the drug, which is linked to 33 deaths worldwide, claimed her life too.

Although banned for human consumption, DNP is easily available online ...

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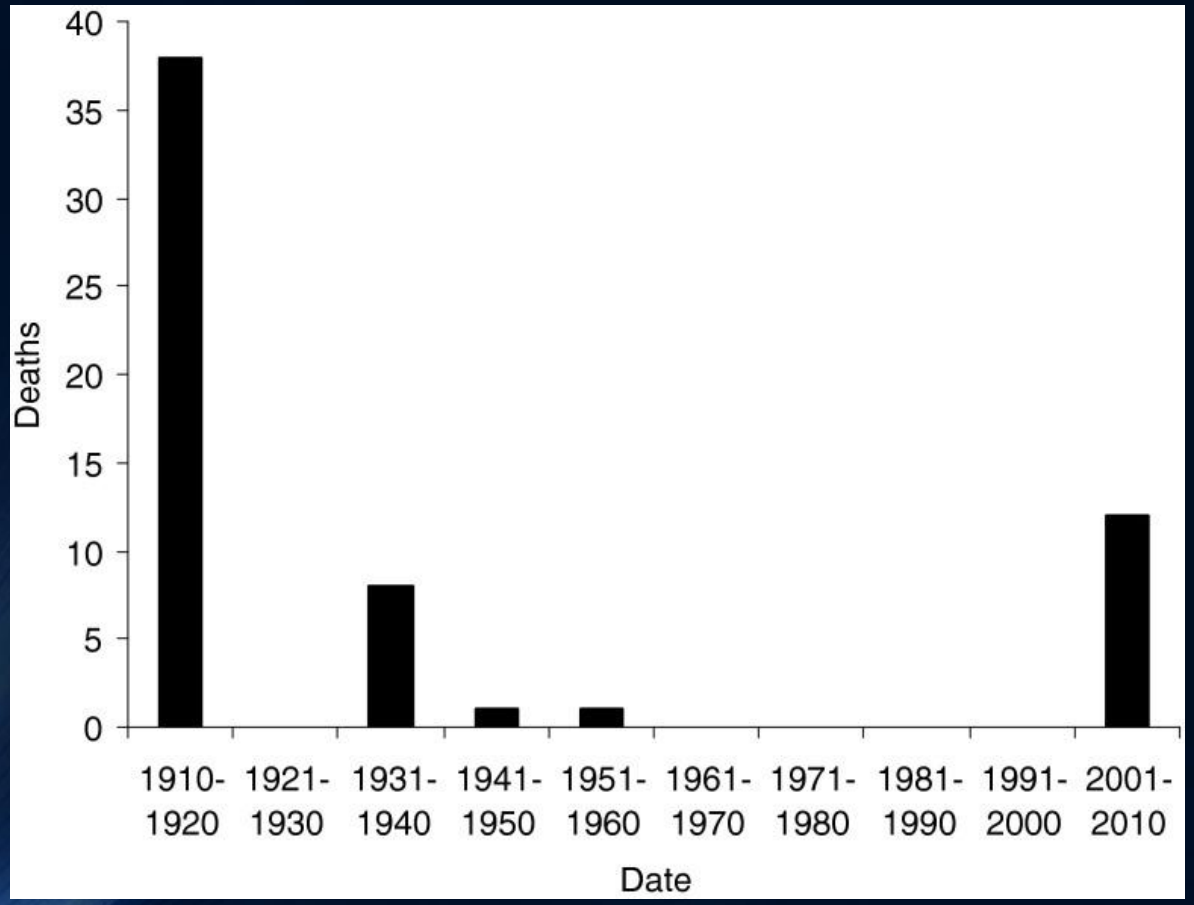
# DNP-related deaths by decade



# Amphetamine: 1932-1968

- Created in 1920's – alternative decongestant to epinephrine
- America's first (iatrogenic) amphetamine epidemic – per person per year consumption similar to present day
- First publication of amphetamine for weight loss NEJM 1938 showed effectiveness
- Initially thought not to be addictive.
  - "…the drugs to which human beings become addicted are the narcotics. There is no evidence in the entire literature of medicine that stimulants become habit forming."
- Used in WWII by pilots to overcome fatigue/boost morale. Weight loss properties discovered

# JAMA 1951

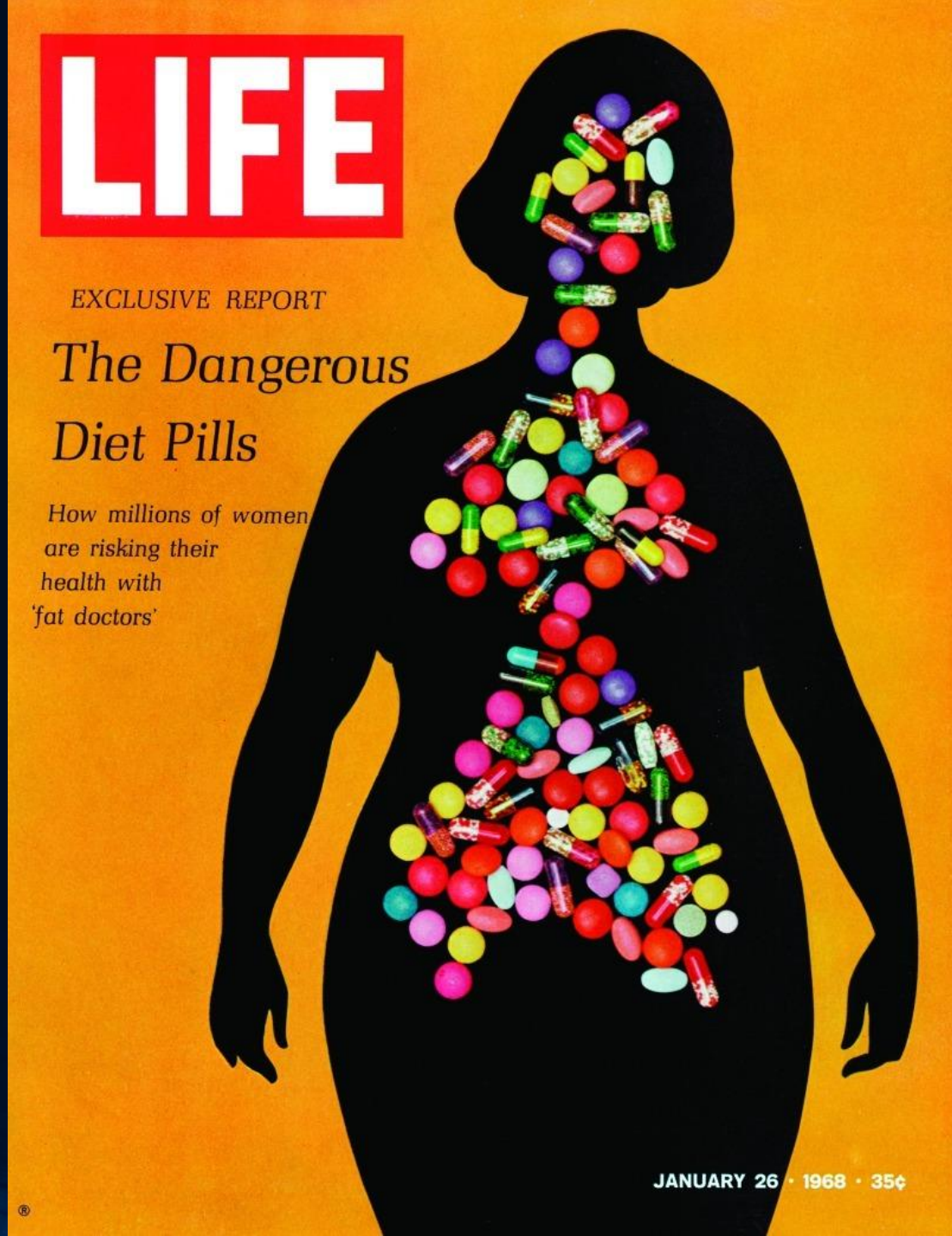

IN MILD PSYCHOGENIC DEPRESSIVE STATES . . .
this
IN MINUTES!
. . . WITH
RAPHETAMINE
PHOSPHATE
Brand of Amphetamine Phosphate
CHEERFULNESS
MENTAL ALERTNESS
OPTIMISM
● Smooth, fast acting Raphetamine Phosphate aids in restoring mental alertness, cheerfulness and optimism in mild psychogenic depressive states . . . and in the management of obesity.
With contraindications chiefly limited to hypertension, cardiac defects, or hypersensitivity to ephedrine-like compounds, benefits may be prolonged.
Newly accepted *parenteral* Raphetamine Phosphate can successfully be used in treating barbiturate intoxication because of its immediate action.
Clinical supply of both dosage forms available on request. Write to Medical Service Department, R. J. Strasenburgh Co., Rochester 14, N. Y.
parenteral: Raphetamine Phosphate, parenteral, containing 10 mg. monobasic racemic amphetamine phosphate per cc. in sterile aqueous solution is available in 10 cc. multidose vials.
tablet: Raphetamine Phosphate tablets containing 5 mg. monobasic racemic amphetamine phosphate per tablet are available in bottles of 100, 500 and 1000.
Strasenburgh
FOUNDED IN 1884

# Rainbow Pills: 1940-1968

- Amphetamines
- Unusual marketing methods. Many color pills.
- Combinations of amphetamine, thyroid hormone, laxatives, diuretics, and digitalis
- Often included one drug to cover side effects of another
  - E.g. Barbiturates and amphetamines
  - Provided directly from doctor offices
- Disappeared from market after Senate hearings in the 1960's.
- Reappeared in 1994 when dietary supplements no longer regulated.
  - Still available via internet. Consumer driven medicine

# Rainbow pills

- LIFE, 1968
- At the time 5000 doctors devoted majority of practice to weight loss



# Anorectic Amphetamine-like Drugs: 1950-1997

- Attempts to separate appetite suppression from stimulant effects
- Phenylpropanolamine For Weight Loss -Accutrim/Dexatrim
  - Patent 1939.
  - Raises BP, constricts vessels—good decongestant
  - Modest weight loss – 0.3 lbs/week long term
  - Raises BP and stroke risk. Removed from market 2000
- Many formulations of Dexatrim
  - Later – ephedra, banned 2004

# Anorectic Amphetamine-like Drugs: 1950-1997

- Aminorex – chemically similar to amphetamine
  - developed by McNeil pharmaceuticals in USA and licensed in 1965 in Europe
  - Serotonin–norepinephrine–dopamine releasing agent (SNDRA)
    - Tripple releasing agent -- Recreational drugs
    - 5-HT are present in the central and peripheral nervous systems, gastrointestinal tract and cardiovascular system
  - Causes pulmonary hypertension ~2% of people who use
  - Hundreds of deaths in Europe. During 1960's 60% of PH patients in Europe had history of aminorex use
  - Withdrawn from market 1972

# Anorectic Amphetamine-like Drugs: 1950-1997

- Fenfluramine 1973
  - Works slightly differently than amphetamines. Alters Serotonin levels
  - 2 Cases of PH described in 1981 – 1st set back. Like aminorex.
  - Not widely used. People did not feel good. Brief weight loss.
- Dexphenfluramine (Redux). ? Fewer side effects 1996-1997
  - Withdrawn for valvular heart disease.
- Phentermine 1959 -
  - Approved 1959.
  - Widely used prior to newer drugs
  - Raises BP

# Anorectic Amphetamine-like Drugs: 1950-1997

- Uses continued and combined phentermine "Fen-Phen" (Pondimin)
  - Two meds, work differently. Never approved in combination. Drugs from 1950 and 1970
  - Sales took off
  - Dramatic weight loss – popular 1990's – 1996, 18 millions scripts in US. Most only overweight by 20 or 30 lbs.
- Valvular heart disease 1997, removed from market world wide
  - Drug induced valvular heart disease – Serotonin. Similar to Carcinoid
    - MDMA, Ergotamine, Fenfluramine. 5HT2b receptor.
  - **Phen**termine – A survivor

# Phentermine/topiramate (Qsymia) 2012 -

- Combination of two medications, phentermine and topiramate.
- Topiramate antiseizure medication
  - Mechanisms: Feelings of fullness and reduced  cravings. Carbonic anhydrase inhibitor.
- REMS program – pregnancy risks. Teratogen
- Responders and nonresponders – stop after 12 weeks if does not lose 5% of body weight.
- Reasonable for people without cardiovascular disease.
- Adverse effects
  - Suicide, heart rate increases, birth defects, seizures on weaning, kidney stones,
  - No CV safety data

# Other Attempts

- Rimonabant
  - Cannabis receptor antagonist
  - Increased suicidality
- Olestra (approved under brand name Olean/WOW) 1996-
  - Food additive. Discovered in 1968. Looking for easier to digest fats for premature infants.
  - Weight loss. Less hunger.
  - Decreases in some serum vitamins
  - Proctor and Gamble sold. Some foods may be available

# Other Attempts – Sibutramine 1997-2010

- Sibutramine (brand name Meridia) was approved by the FDA in 1997 for weight loss and maintenance of weight loss
- Increases levels of serotonin and norepinephrine in the brain, helping to reduce appetite.
- Removed from market due 2010 to increased rates of heart attack and stroke
- 2012 FDA finally decides to require obesity medications have appropriate designed studies to assess CV endpoints

# Orlistat 1999

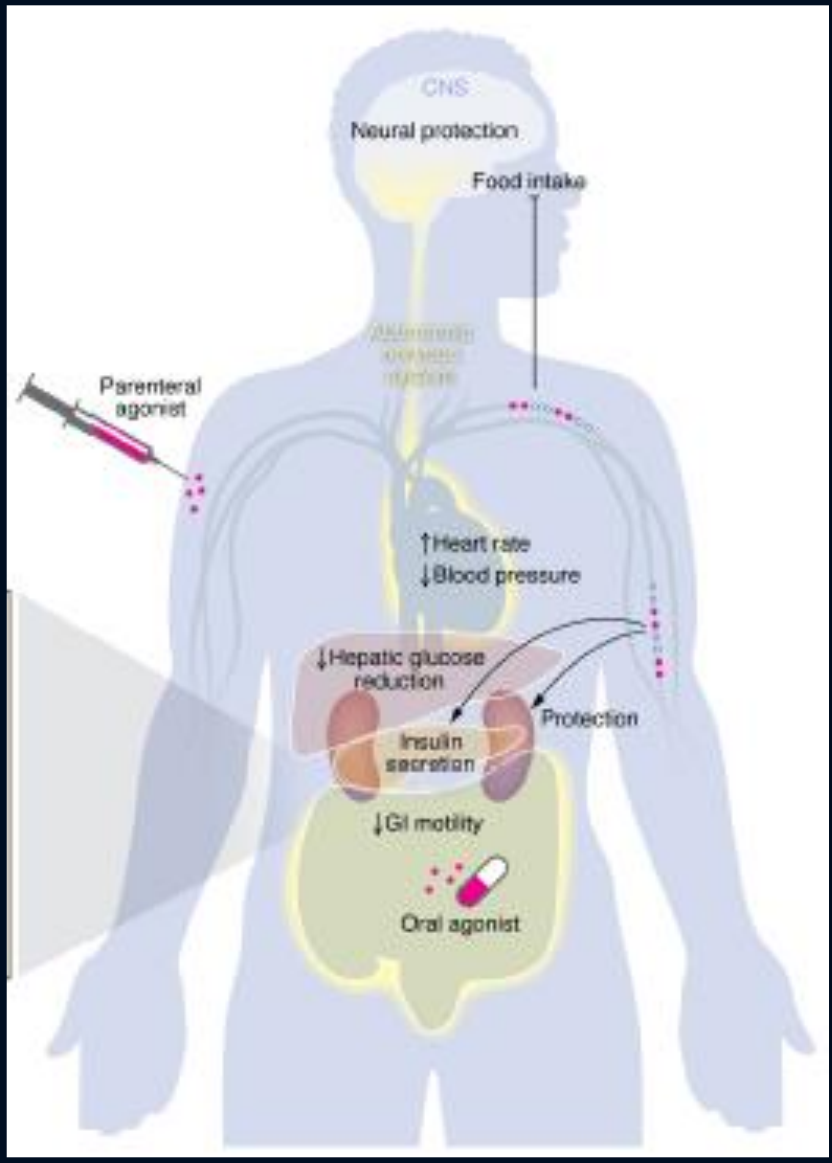
- Approved in 1999
- OTC in 2007 (Alli)
- Inhibits pancreatic lipase – reduces absorption  % of dietary fats
- Inhibiting the absorption of approximately 25 to 30 percent of calories ingested as fat
- Effective but many GI symptoms. Use with multivitamin.
- RCT data suggests favorable impact on BP, lipids, a2c

# Naltrexone/bupropion (Contrave) 2014 -

- Combination of two medications, naltrexone and bupropion
- Naltrexone blocks opioid receptors. Used to treat alcohol and opioid dependence
- Bupropion is an antidepressant and smoking cessation aid
  - norepinephrine- and dopamine-reuptake inhibitor
  - Increases energy expenditure
  - Decreases appetite
- Monitor for suicidal thoughts and behaviors. Can lower seizure threshold. No CV safety data.

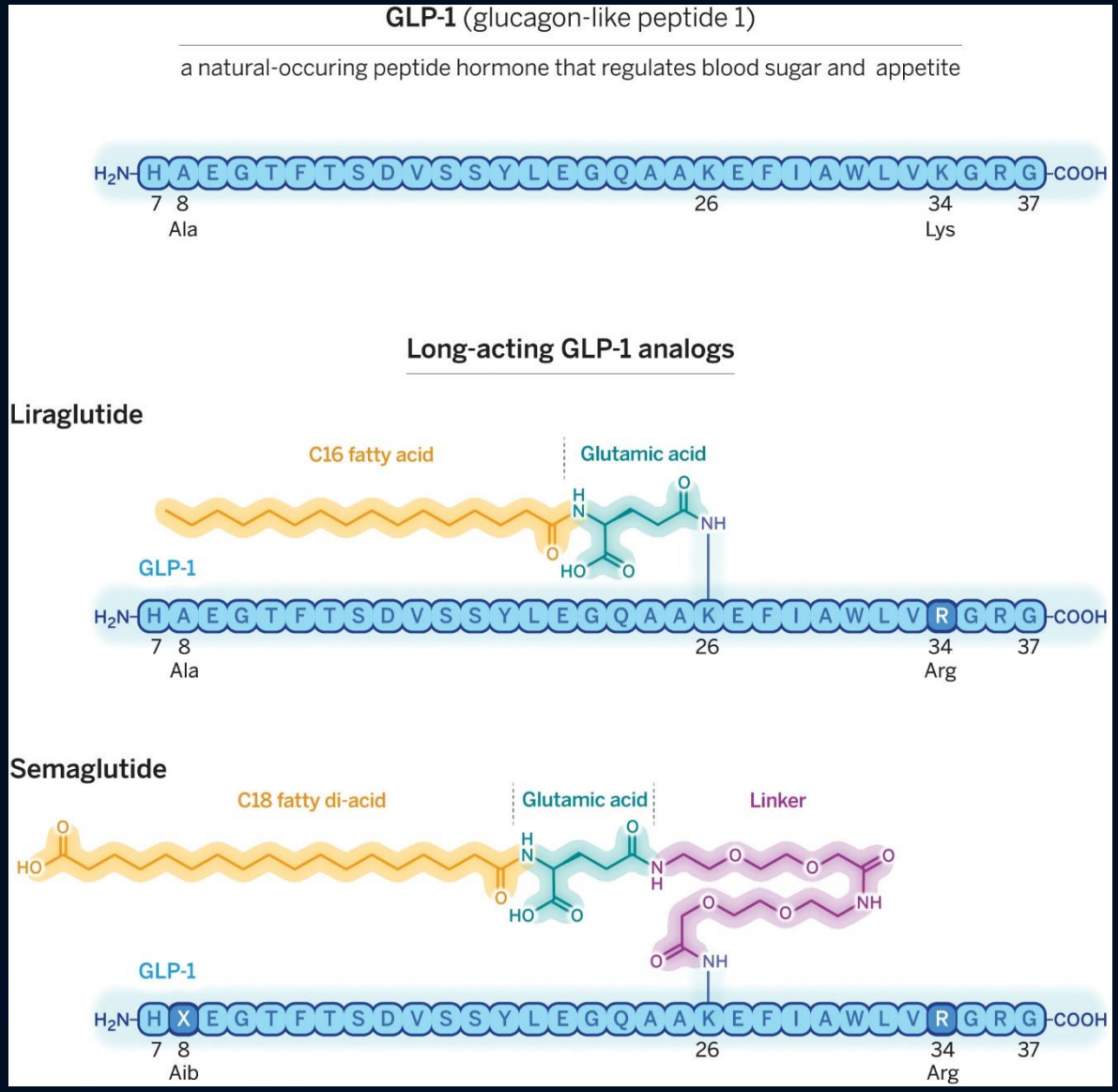
# The Rise of GLP-1s

- 1906 – Intestine extract could lower glucose. Name "incretine"
- Incretine
  - Released from gut with eating
  - Stimulates insulin production
  - **Only works in presence of high sugar levels
- Took until 1986 for an MGH endocrinologist to discover that incretine was Glucagon like peptide-1 (GLP-1)



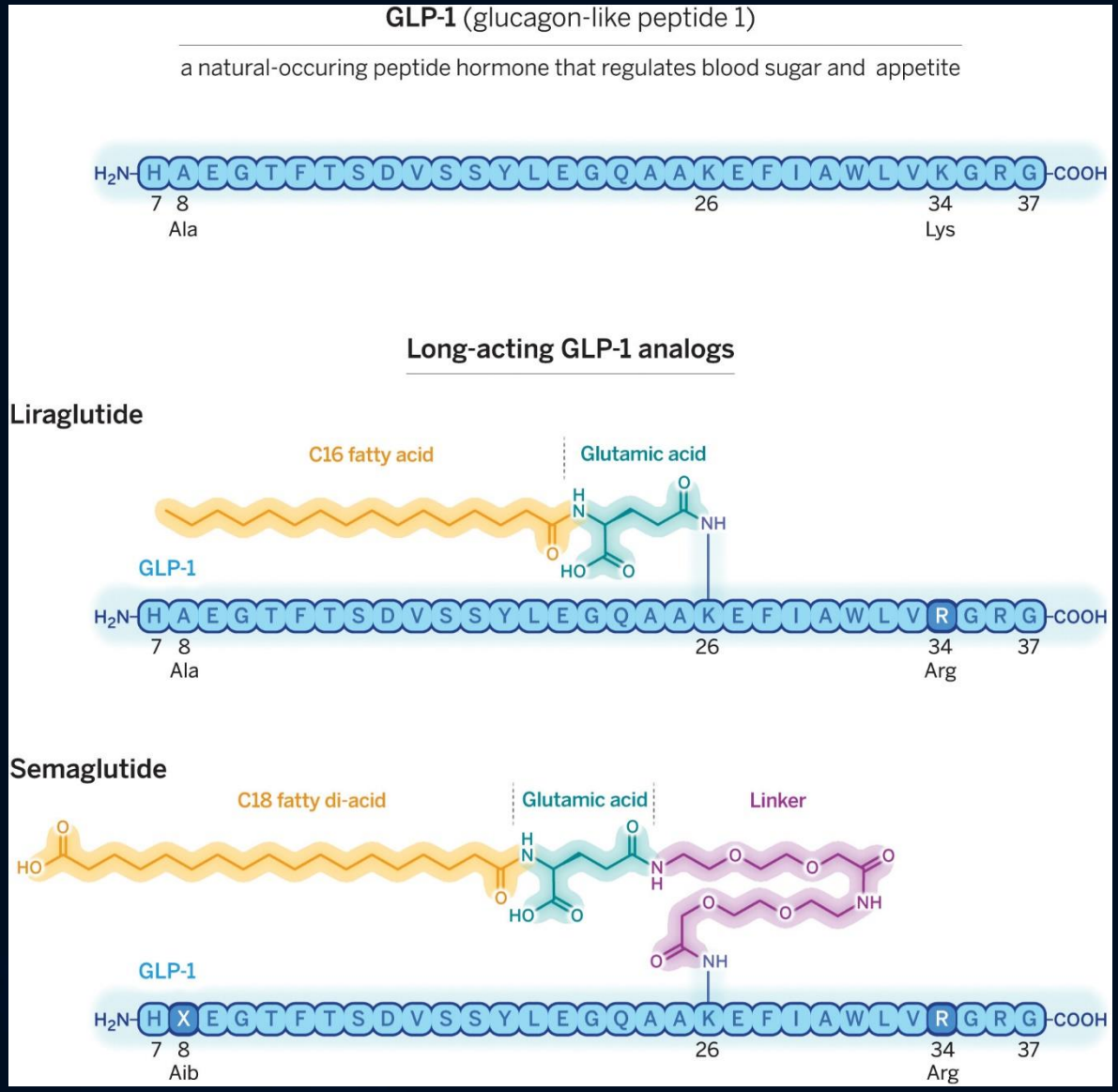
# The Rise of GLP-1s

- 1987 – Seven human volunteers, GLP-1 infusion found to increase insulin those who received glucose *but not in those who fasted.*
- 1992 Shown to be effective to treat diabetes.
- PROBLEM – Half life is 1 to 2 minutes
  - Novo Nordisk changed molecule. Bind protein but not too different to be immunogenic
  - Saxenda (Liraglutide) 2014, half life 13 hours



# The Rise of GLP-1s

- Initial studies disappointing
  - Nausea. Needed to reduce dose. Not much weight loss.
- Key discovery 2010. Nausea overcome by starting low and increasing dose. Trials redesigned
- Other companies begin to compete with Novo Nordisk



# Rise of GLPs

- 1980's NIH – experiments with animal venom found proteins that stimulate the pancreas.
- Venoms contain many proteins – distinct from poison -- designed to disruptive biologic systems.
- Eng and Rothman – Bronx VA. Discovered Exendin-4, resembled the human hormone GLP-1, in Gila Venom.
- Only stimulates insulin production when glucose is high. In contrast to human GLP-1, lasts for hours!

# Rise of GLPs

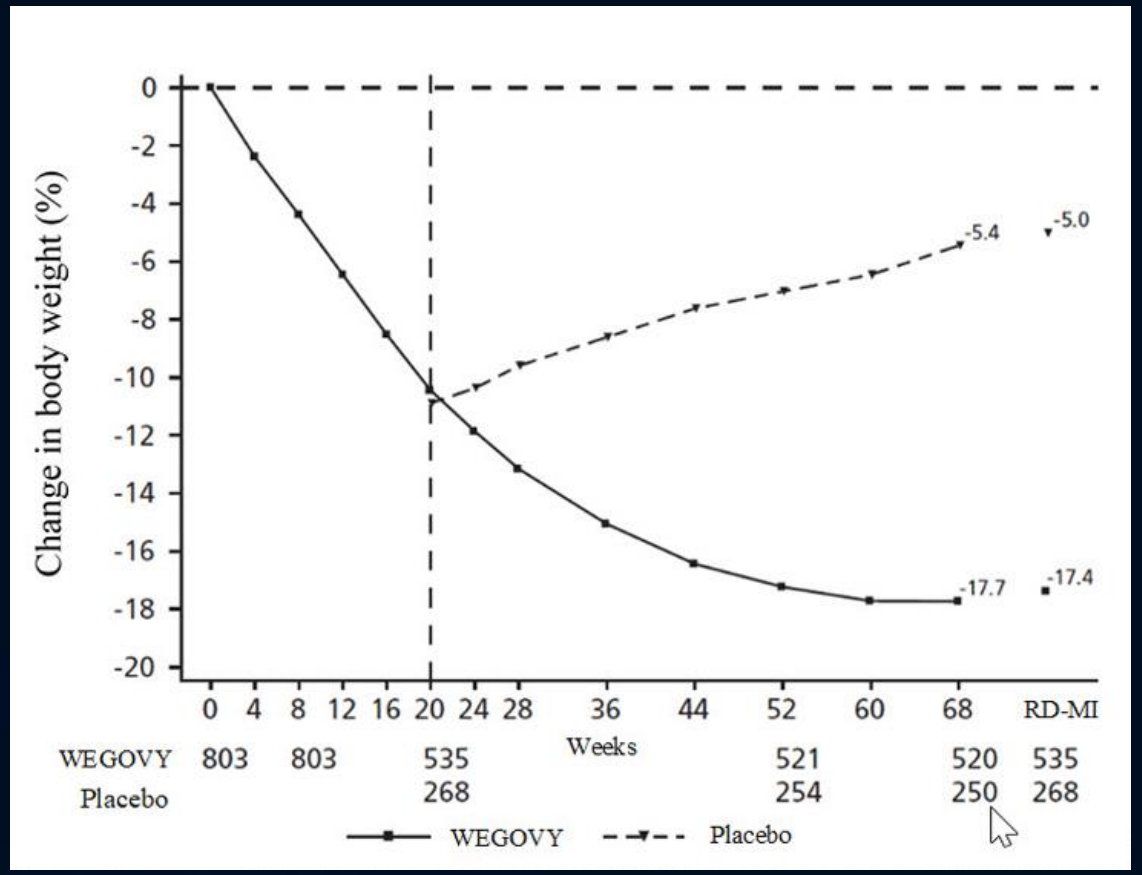
- Extendin-4. VA would not patent. Eng persisted. Licensed patient to a startup for less than 1m.
- In 2002, Eli Lilly paid $325 for the patent.
- Exenatide (Byetta) approved for diabetes in 2005.

# Modern Era

| Generic | Weight loss | Diabetes |
|---|---|---|
| Semiglutide | Wegovy | Ozempic / Rybelsus |
| Tirzepatide | Zepbound | Mounjaro |
| Liraglutide | Saxenda | Victoza |

# GLP-1 Concerns and Unanswered questions

- Nausea significant and some patients can not tolerate
- Need to be taken continuously to be effective
- Treatment leads to fat AND muscle loss (equivalent to that seen with dieting)
- Muscle mass does not recover when drug stopped
- Possible association with some cancers
- Use in patients for 20 years, but vigilance required



# GLP-1 Unanswered questions

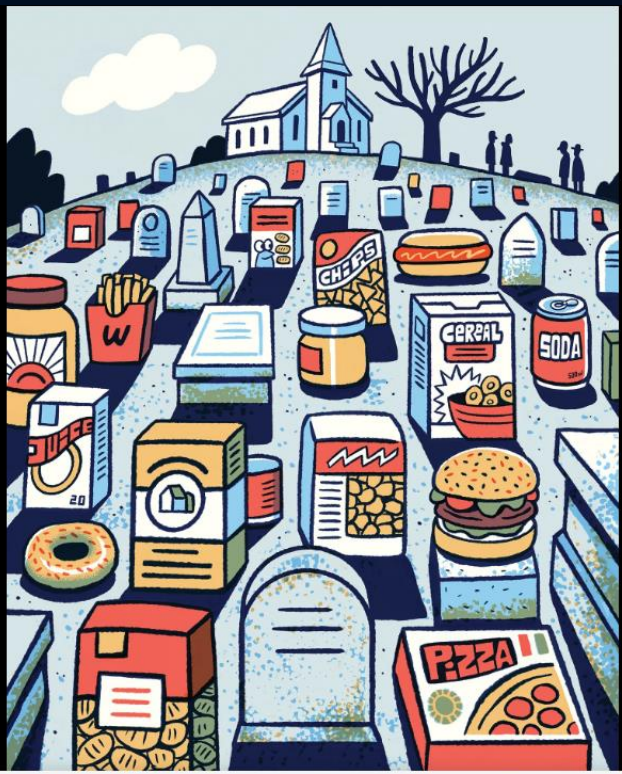
- Eating for energy vs. hedonism
  - Traditionally viewed separately
  - Early GLP data shows these are linked with metabolic hormones influencing pleasure centers
  - Eating leads to dopamine release in the brain. GLP reduces this dopamine release
    - Same pathways active in shopping, gambling, smoking, drug use, sex, and alcohol -- Role of dopamine and GLP?
    - Area of active study
  - Weight-loss medications like GLP-1s don't just affect hunger and metabolic dysfunction—they influence how the brain processes reward. Turns down reward
  - Allocation, fairness, and cost

# GLP side effects

- Contraindications and precautions:
  - personal or family history of MTC or MEN2. Pregnancy
  - History of pancreatitis (conflicting data)
- Side effects
  - GI
  - Pancreatitis
  - Worsening retinopathy
  - Cholelithiasis and cholecystitis (higher doses, longer treatment)

# Future directions

- Oral agents
- Other gut hormones showing promise
- Causes of epidemic

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