

Obesity



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October 19, 2015

Disclosures

I receive **research funding** from the U.S. National Institutes of Health and Ethicon

I am a member of **scientific advisory boards** for the following companies:

Astra-Zeneca	Ethicon	Fractyl	Gelesis
GI Dynamics	Janssen	MedImmune	Novo Nordisk
Pfizer	Raziel	Rhythm	USGI Medical
Zafgen			

I am a member of **scientific advisory boards** for the following organizations:

Nutrition Science Initiative	AGA Microbiome Institute
National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)	

I have **equity** in the following companies:

Fractyl	Gelesis	GI Dynamics	Rhythm
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I may discuss the **off-label / unapproved use** of several drugs and devices, including bupropion, canagliflozin, EndoBarrier, exenatide, intragastric balloon, liraglutide, metformin, naltrexone, phentermine, pramlintide, topiramate and zonisamide

What is Obesity?

Excessive fat accumulation
that presents a risk to health

- The presence and severity of obesity can be *measured* by body composition analysis and *estimated* by a variety of biomarkers
 - Body mass index (BMI)
 - Body fat distribution
 - Risk scores
 - Comorbidities
- But these markers **should not define** obesity



Arguments that Obesity is **NOT** a Disease

- It is a lifestyle choice
- No specific symptoms associated with it
- It is a **risk factor** for disease, not a disease itself*
- Calling it a disease would define one-third of Americans as being ill and could lead to more reliance on costly drugs and surgery rather than lifestyle changes**

* What about high cholesterol or hypertension?

** What about the combined prevalence of hypertension, dyslipidemia, and diabetes?

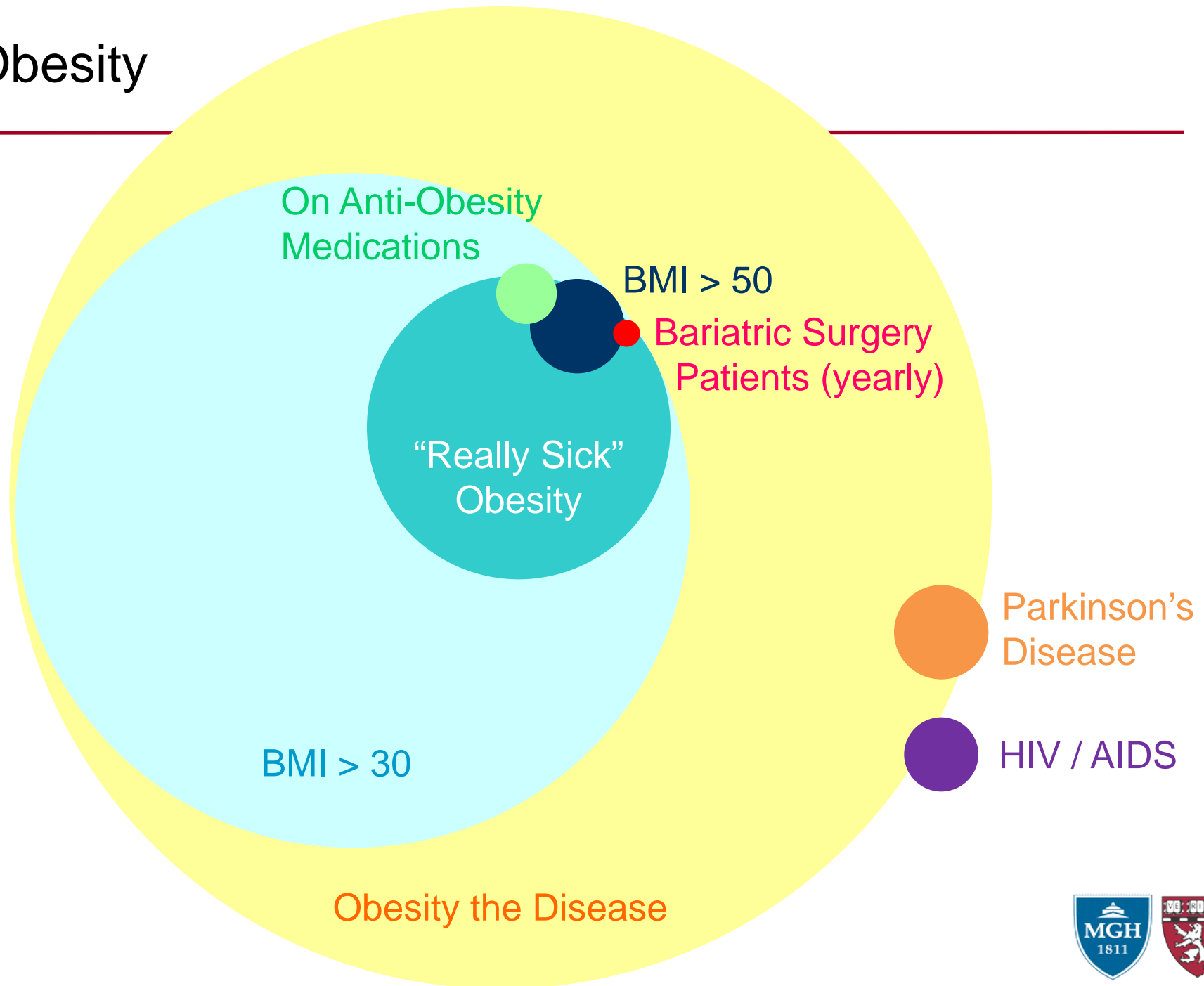


Why Obesity **IS** a Disease

- It is associated with impaired body function
- Like other diseases, it results from physiological dysfunction (precipitated by numerous forces in modern society)
- It causes, exacerbates or accelerates more than 180 significant comorbid diseases
- It is associated with a substantial burden of morbidity and premature death



Obesity



Medical Complications of Obesity

Metabolic

Structural

Inflammatory

Degenerative

Neoplastic

Psychological

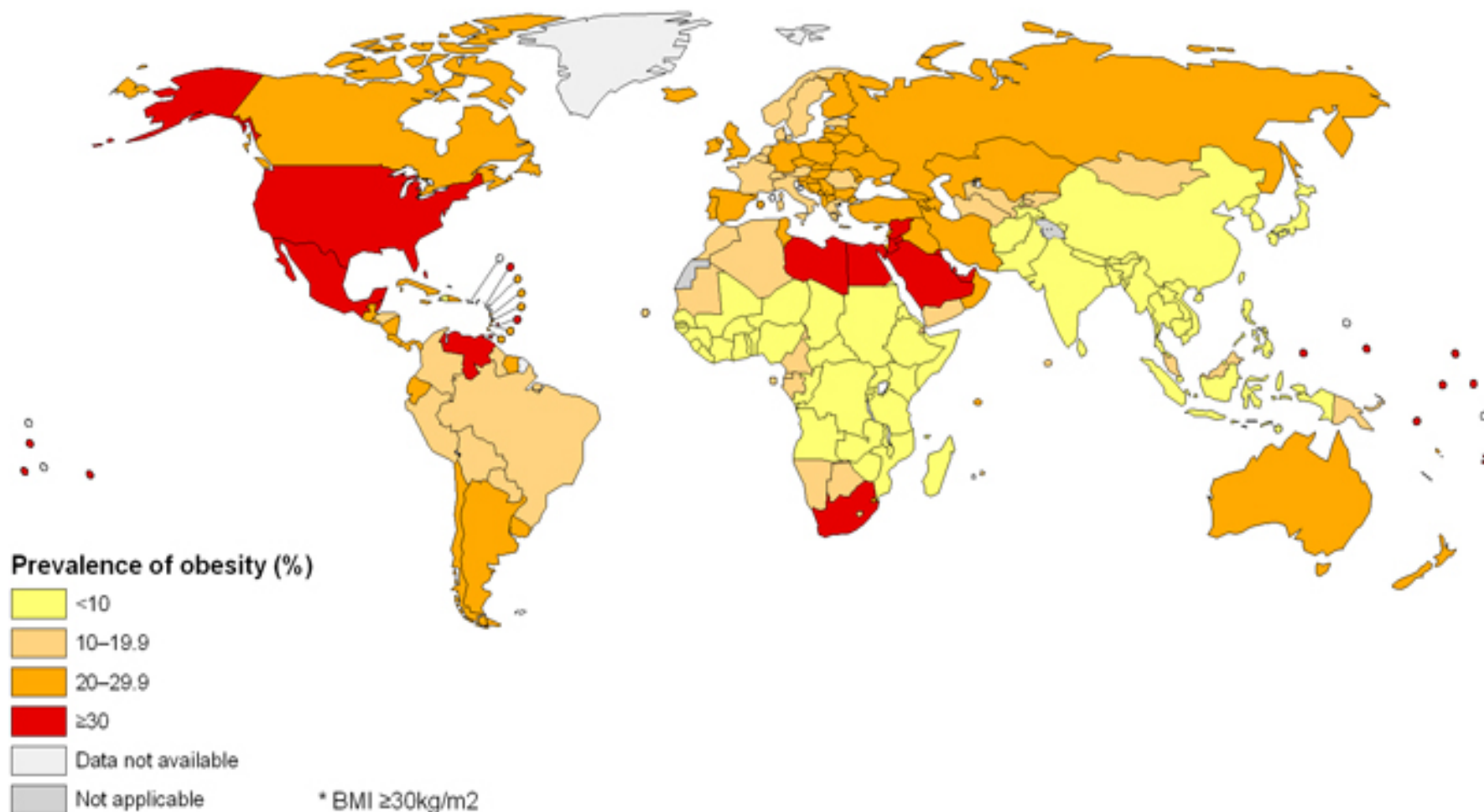
180

Obesity is Counterintuitive

- Hides in plain sight
 - Most obesity **NOT** recognized by physicians or the public
- Did **NOT** start in the past 30 years
- **NOT** a problem of eating too much
- **NOT** a single disorder
 - Several dozen or more clinically meaningful subtypes
 - This recognition is essential to solving the problem
- The problem is **NOT** slowing down
- **NOT** mainly in America

Obesity is a Worldwide Epidemic

2008



Obesity

Historical view

- Lifestyle choice
- Characterological flaw (willpower, psychology, morality)



Obesity

Historical view

- Lifestyle choice
- Characterological flaw (willpower, psychology, morality)

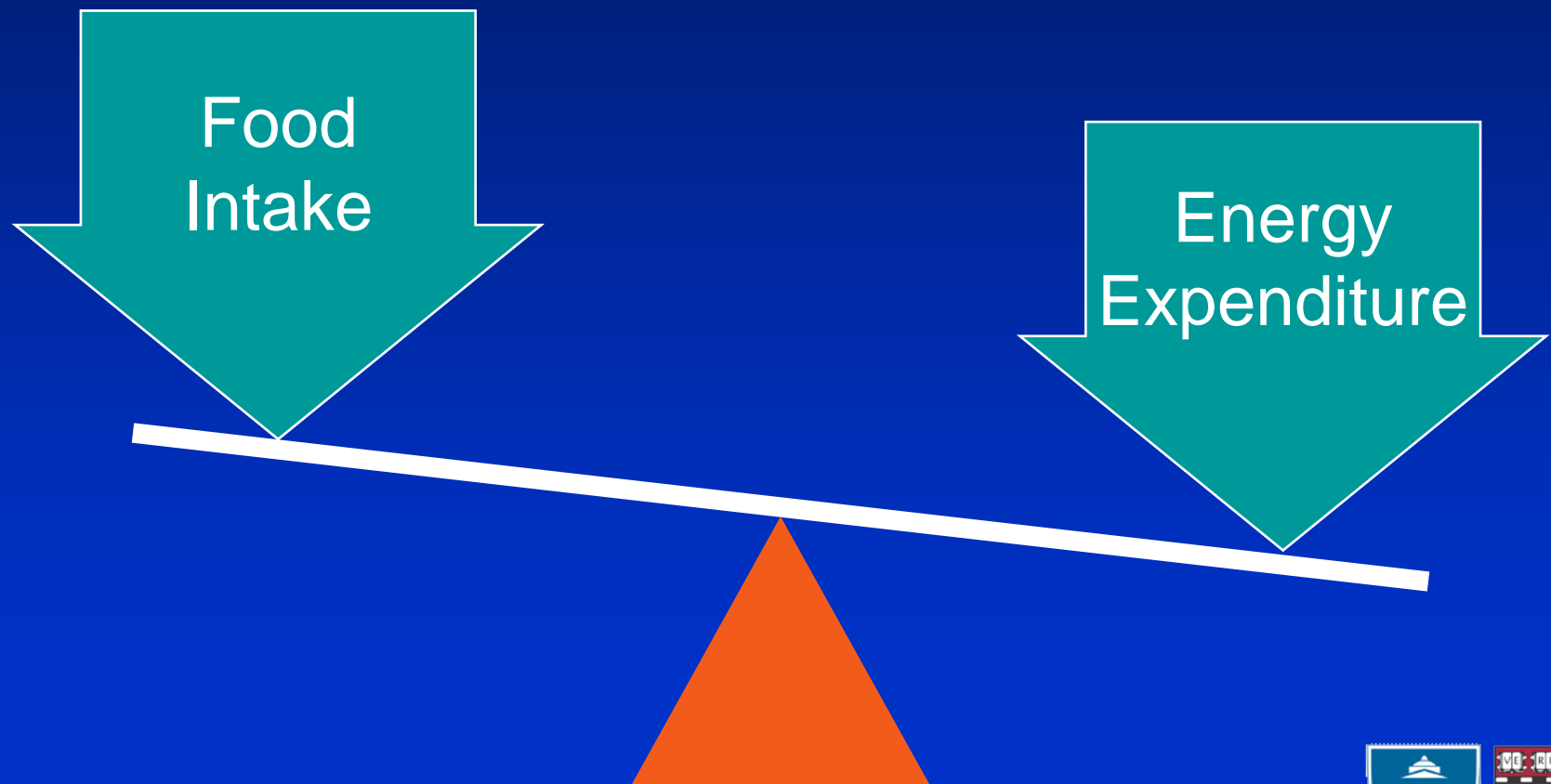
Current perspective

- Dysfunction of a complex physiological regulatory system
- Widely recognized as a disease
- Devastating effect on efficacy and quality of life



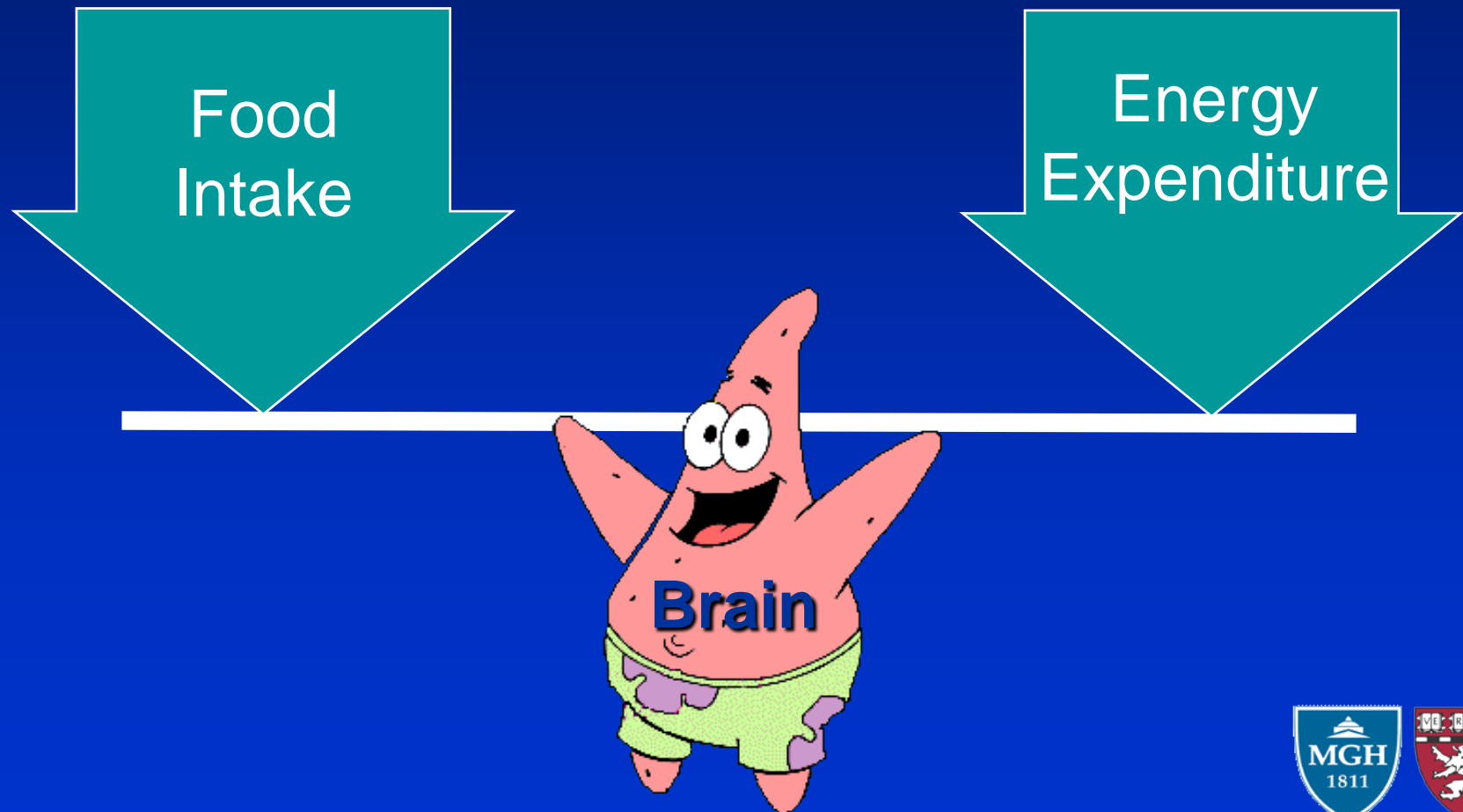
Weight and Energy Balance

By the laws of physics...

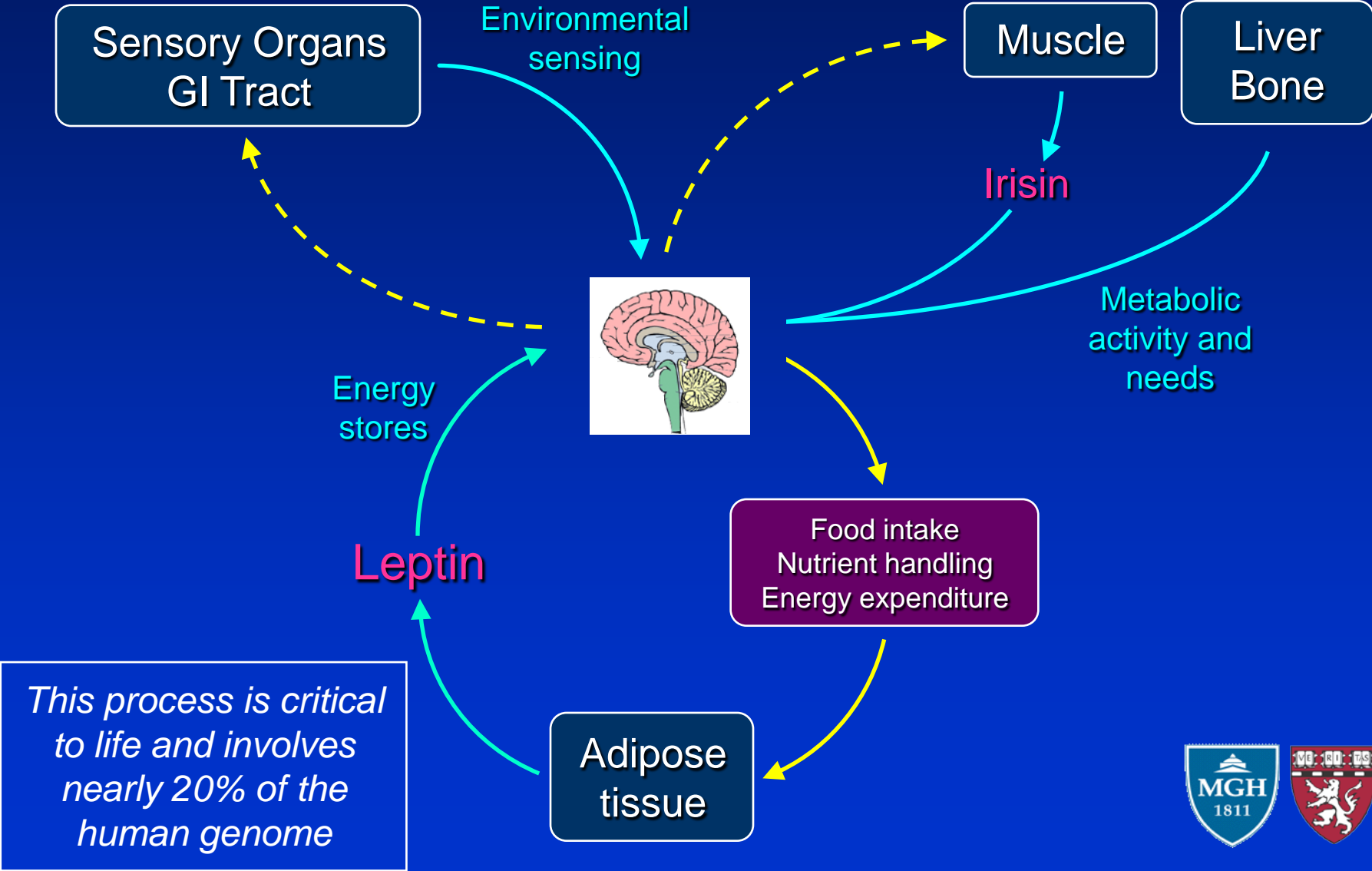


Weight and Energy Balance

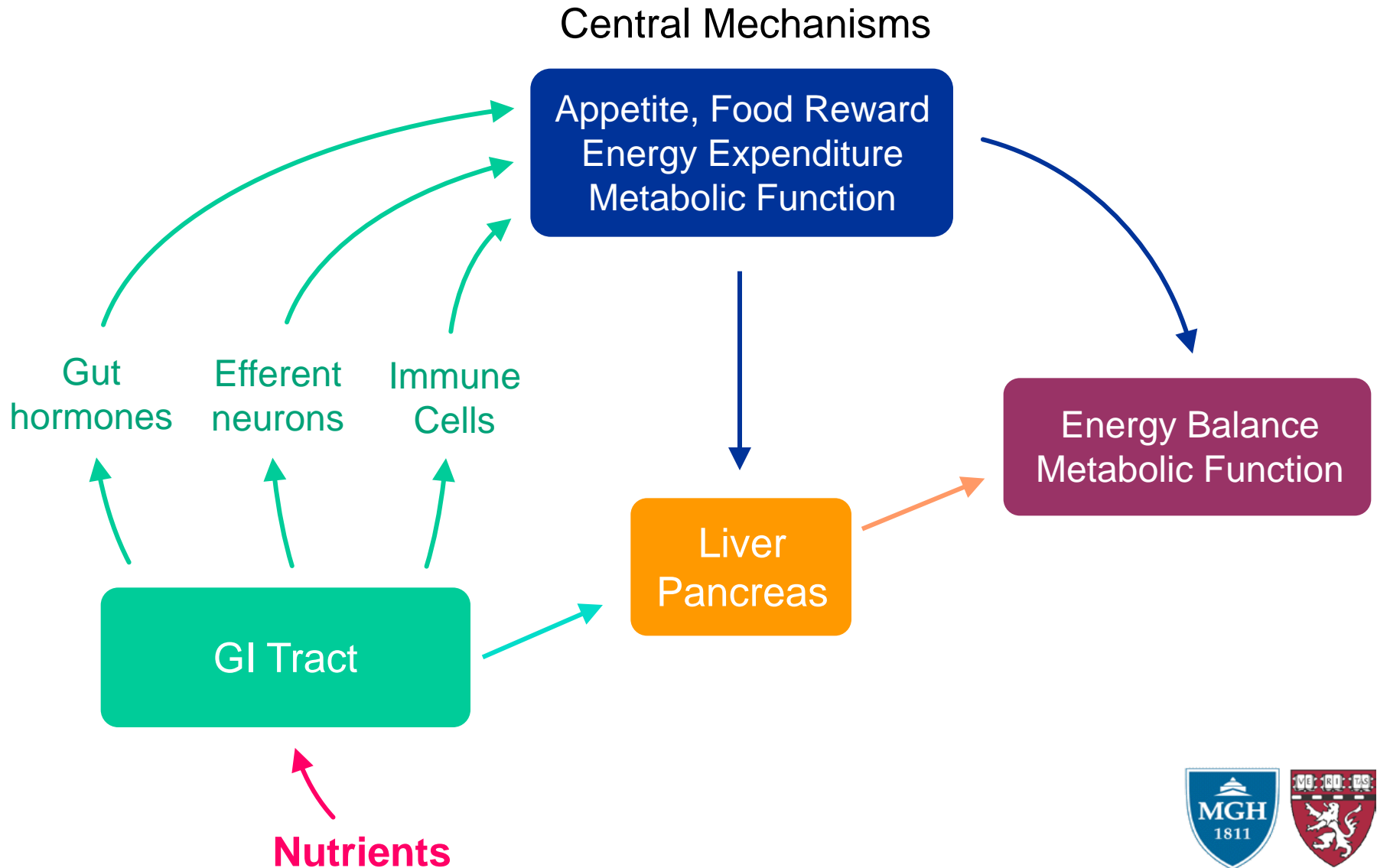
Adding physiology to physics...



Feedback Regulation of Energy Metabolism



GI Regulation of Metabolic Function

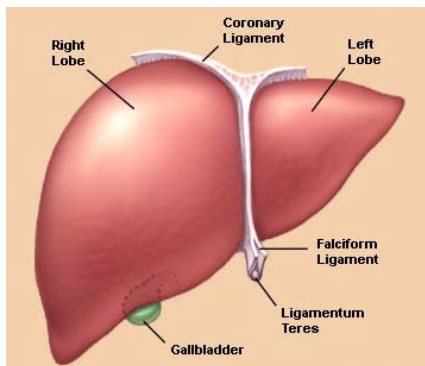


The Body Seeks a Stable Adipose Tissue Mass



Similar to other regulated tissue mass

- Liver
- Red blood cells



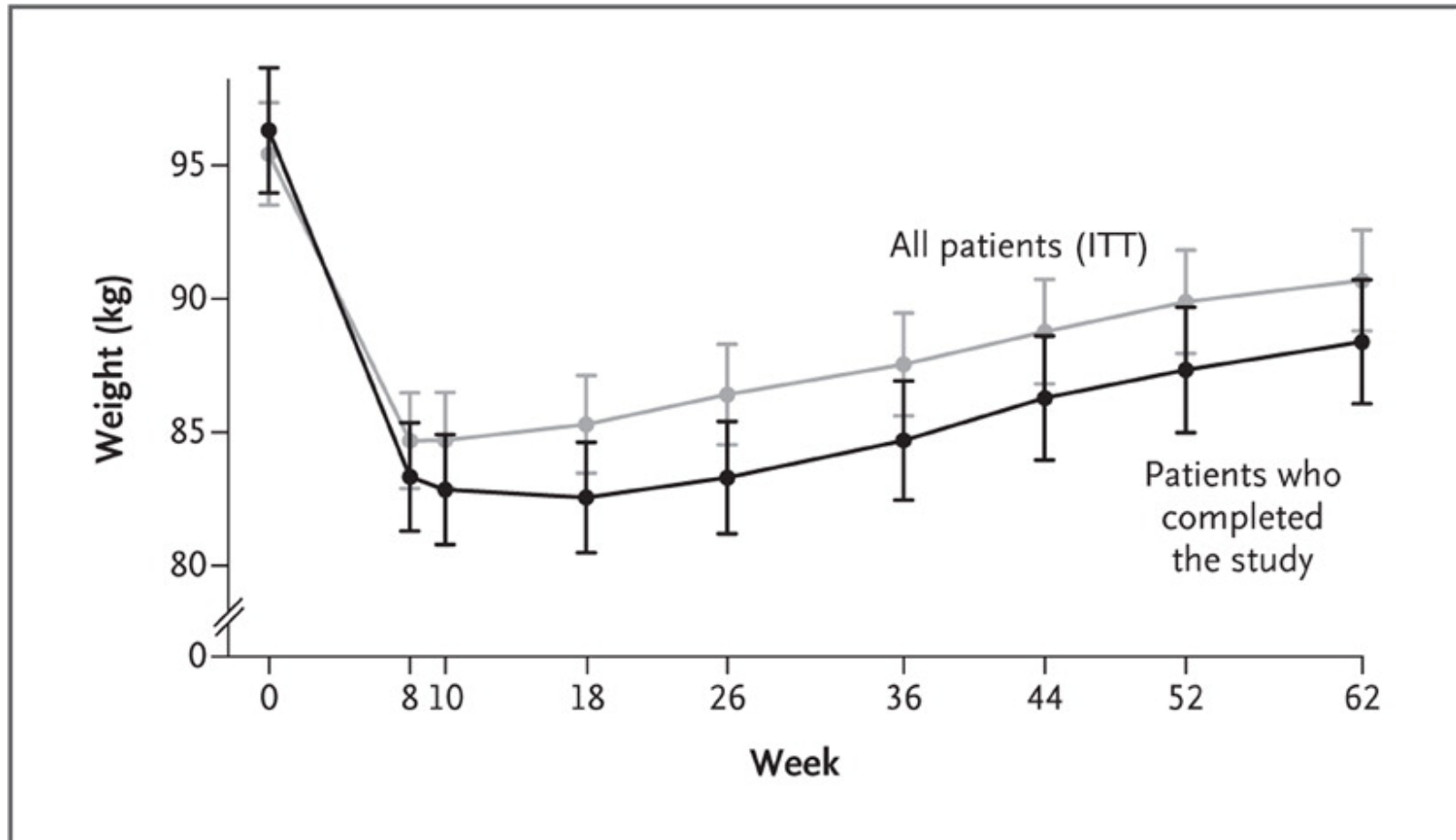
The Normal Physiology of Energy Balance

- Average adults **require** approximately 1300 kcal/day*
- Average adults **consume** 2000-2500 kcal/day
 - Average adults thus consume 1.5-2 times as much food as needed
 - Excess intake is available for physiological emergencies
- Maintenance of normal fat stores (and body weight) **requires precise disposal** of 40-50% of ingested calories daily
- Maintaining weight within 20 lbs. between ages 21 and 65 requires **matching of intake and expenditure within 0.2%**
 - Corresponds to accuracy of 4-5 kcal/day
 - Less than one-half potato chip



Thus, daily *energy balance* must be a tightly regulated physiological trait

Why is Weight Regain So Prevalent?

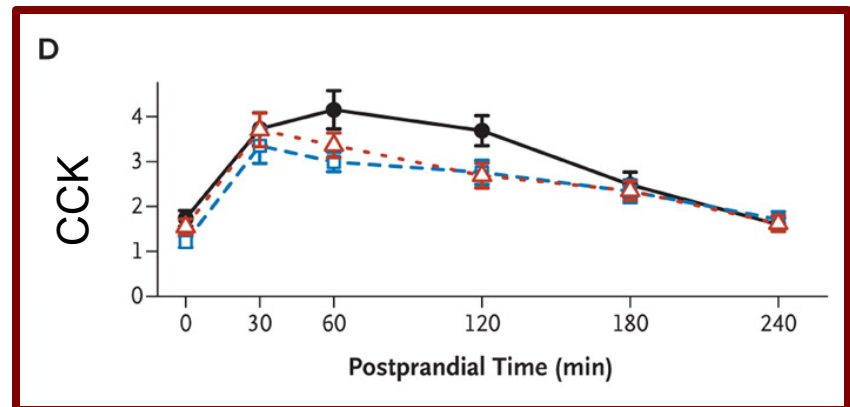
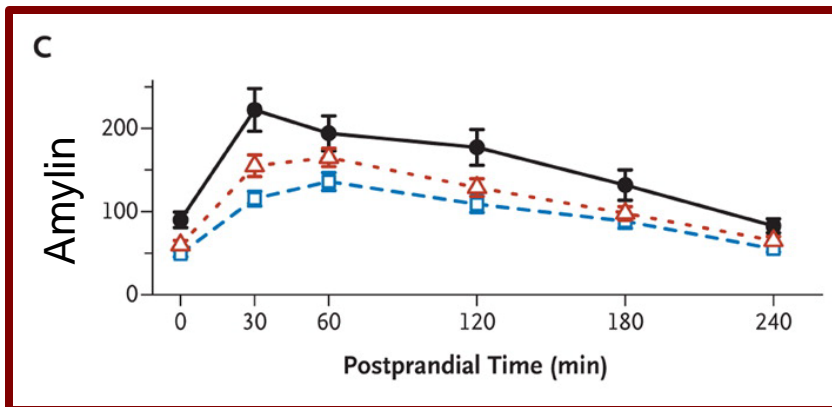
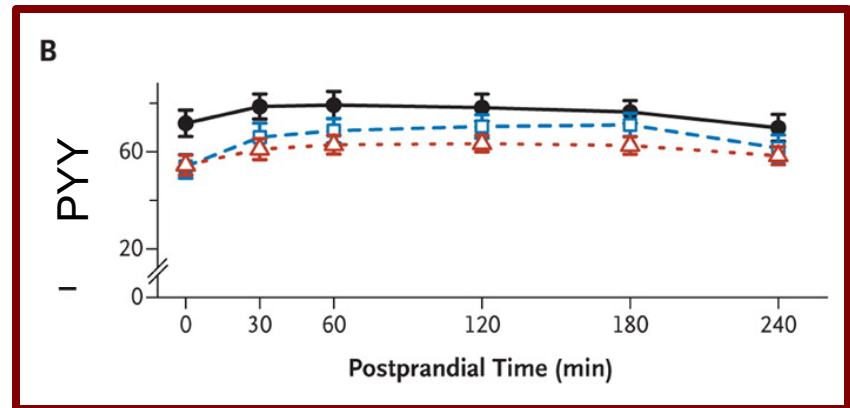
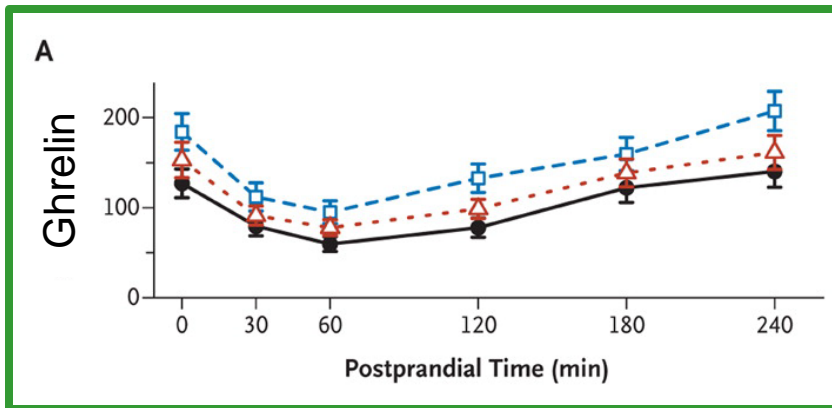


Sumithran et al. NEJM 2011; 365:1597-1604.



Gut Hormone Changes Persistently Oppose Diet-induced Weight Loss

—●— Baseline - -□- Week 10 - -△- Week 62

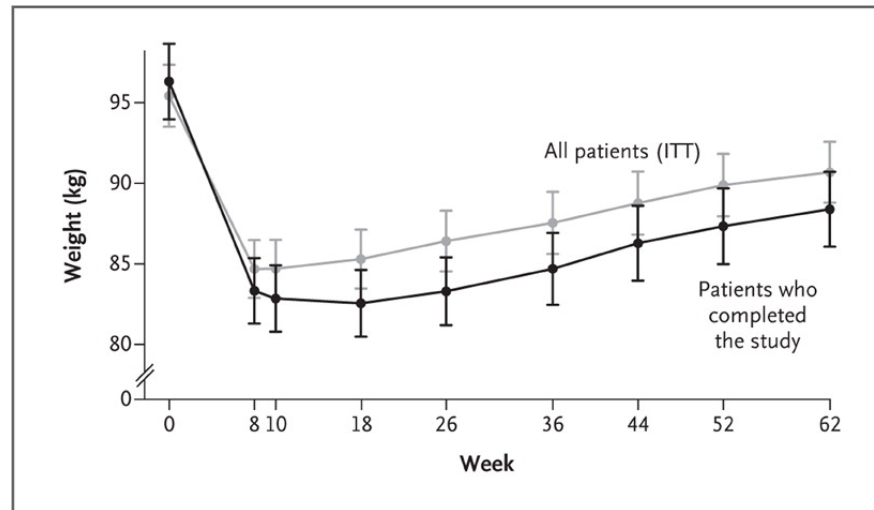


Obesity results from a failure of normal weight and energy regulatory mechanisms...

...leading to an elevated body fat set point



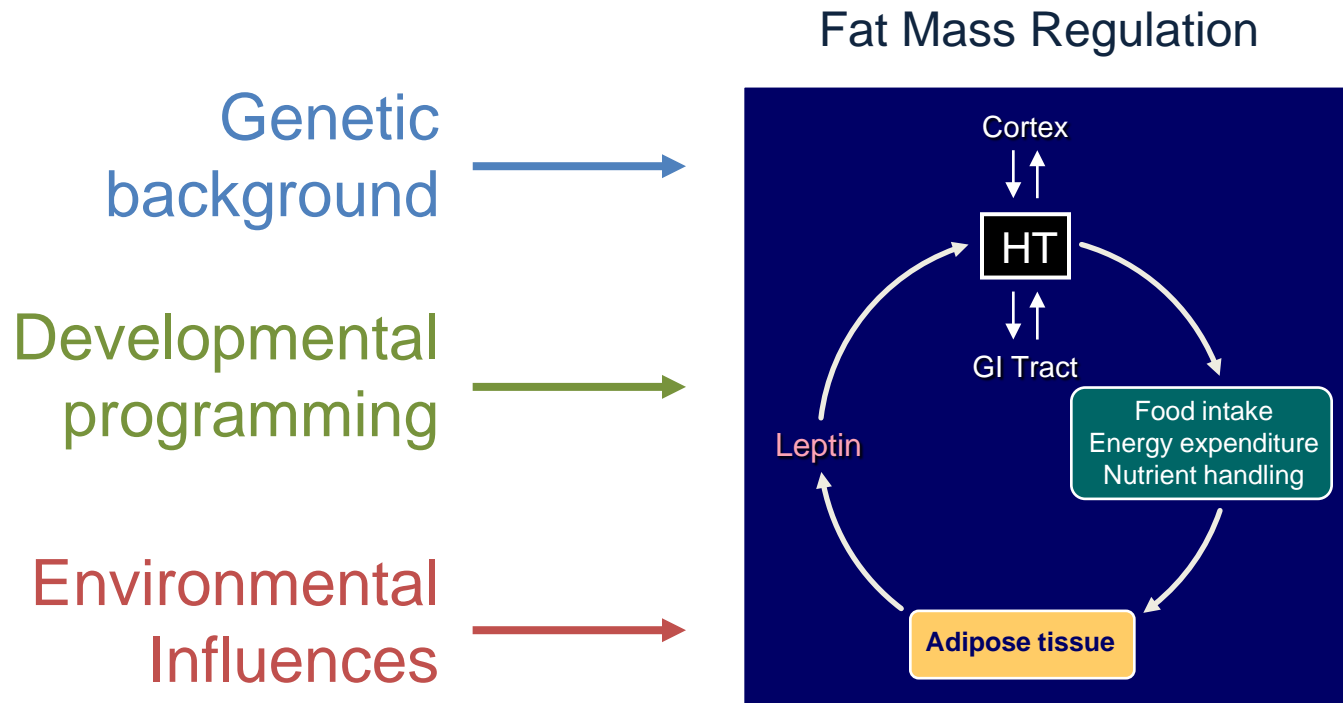
Why Defend the Fat Mass?



- The body **needs** to defend a fat mass set point
 - To shed the excess calories consumed daily
 - To recover appropriately from acute illness or injury
- The body **defends** its fat mass set point
 - Even if it is abnormally high (i.e., obesity)

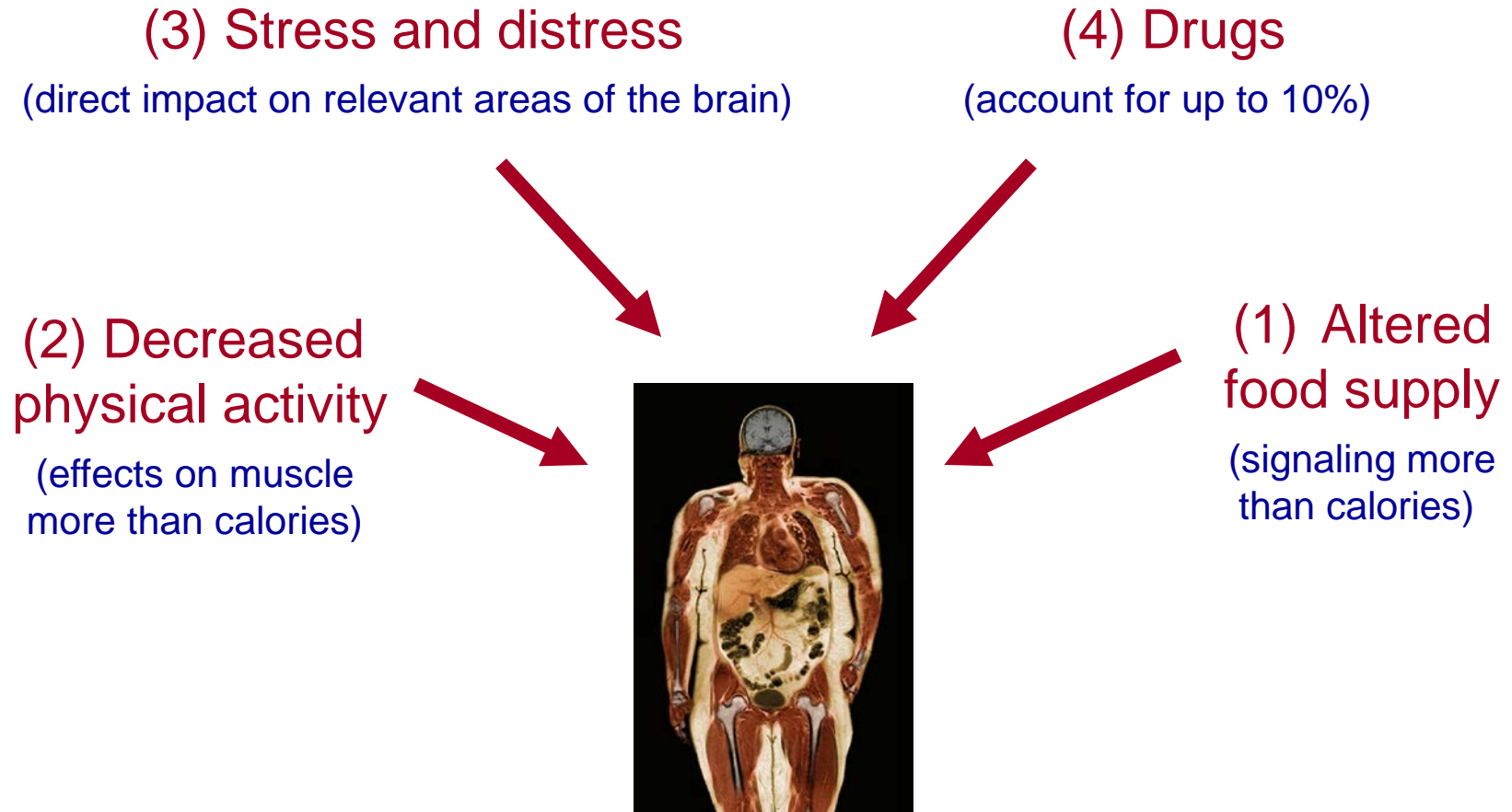
Obesity results from a failure of normal weight
and energy regulatory mechanisms

Obesity: A Physiological Regulatory Error



The current obesity epidemic results primarily from changes in the modern **environment**.
So what are those changes?

Environmental Drivers to Obesity



These influences act by **raising** the fat mass set point

Obesity Treatment



Obesity Treatment Strategy

Stepwise Approach

(progress through algorithm as clinically required)

Post-surgical Combinations

Weight Loss Surgery

Pharmacotherapy

Professionally-directed Lifestyle Change

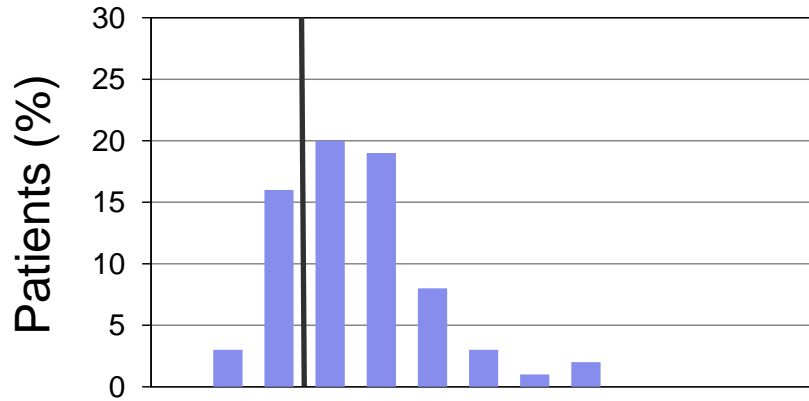
Self-directed Lifestyle Change

Core Principles of Obesity Treatment

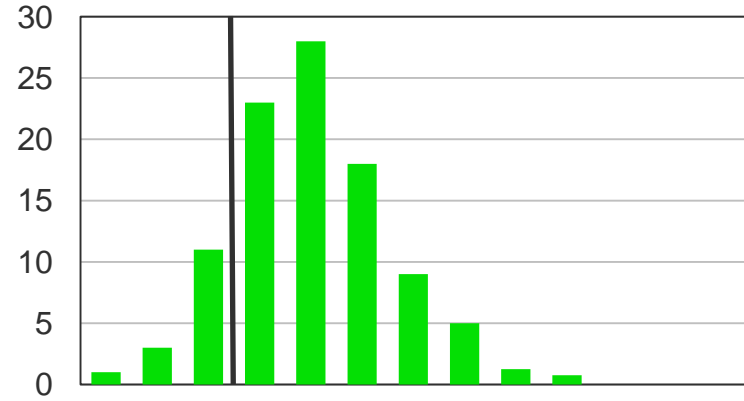
1. The goal of effective treatment is to **reduce the elevated fat mass set point**
2. There is **wide heterogeneity** in the causes and manifestations of obesity
3. This leads to **wide patient-to-patient variability** in the response to all anti-obesity therapies

Weight Loss Varies Widely Among Patients

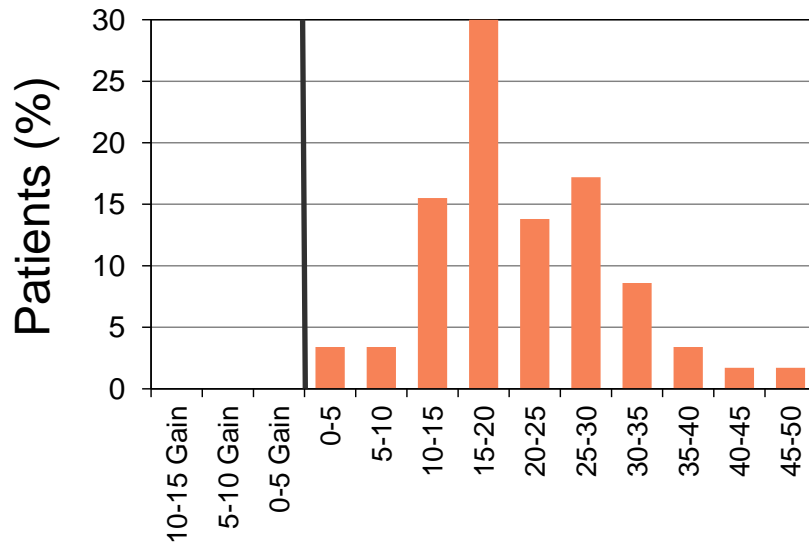
Diet (Low-carbohydrate)



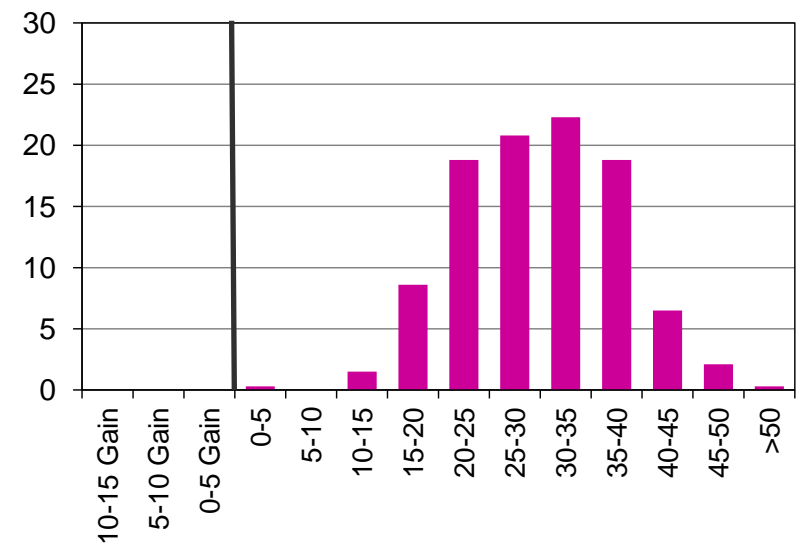
Drug (Liraglutide)



Device (Duodenal liner)



Surgery (Gastric Bypass)



Core Principles of Obesity Treatment

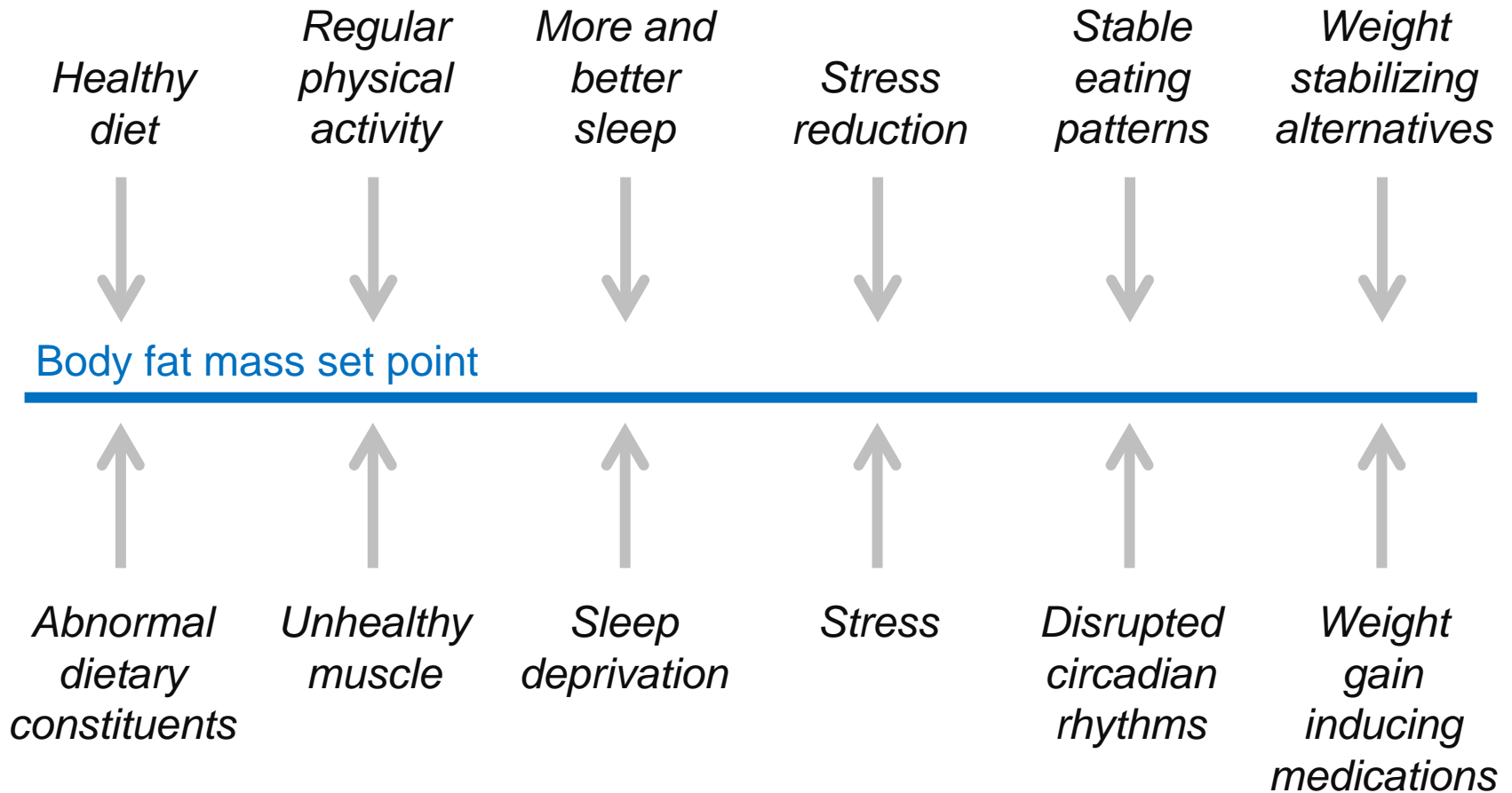
1. The goal of effective treatment is to reduce the elevated fat mass set point
2. There is wide heterogeneity in the causes and manifestations of obesity
3. This leads to wide patient-to-patient variability in the response to all anti-obesity therapies
4. People who respond to one therapy may not respond to another, and vice versa
5. The strategy is to match each patient with the treatment most effective and suited to them



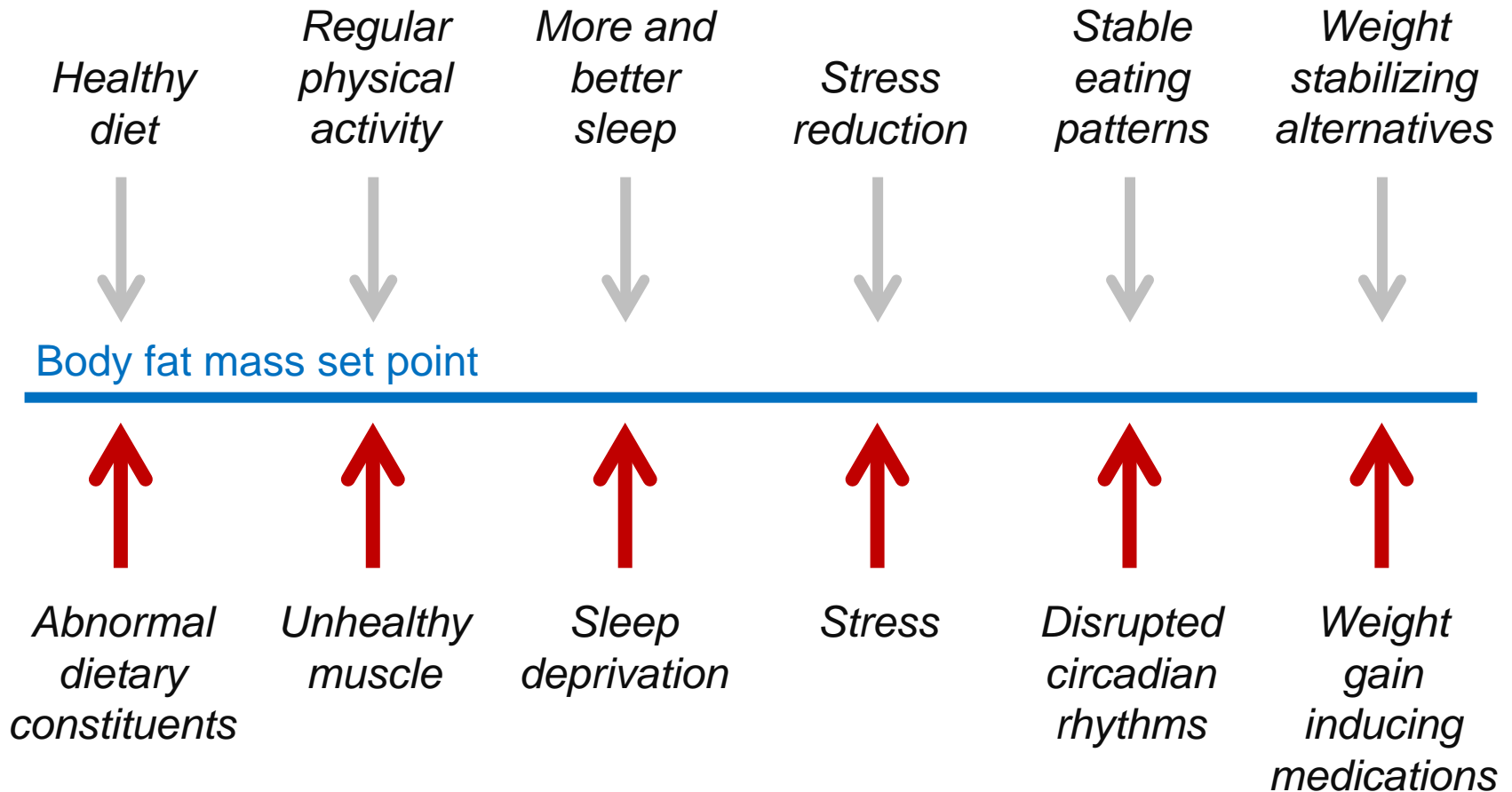
Wide variability in therapeutic response is best explained by clinically important subtypes



Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point



Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

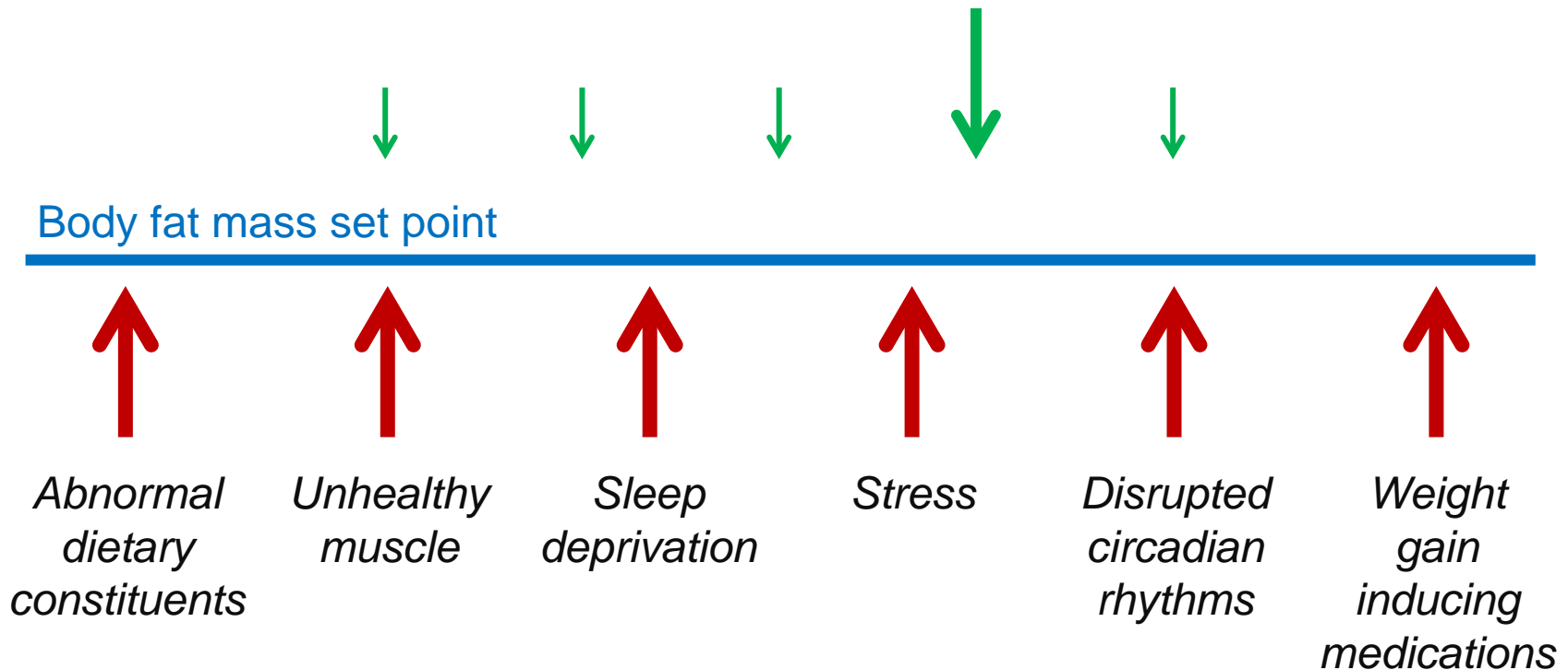


Years of Exposure

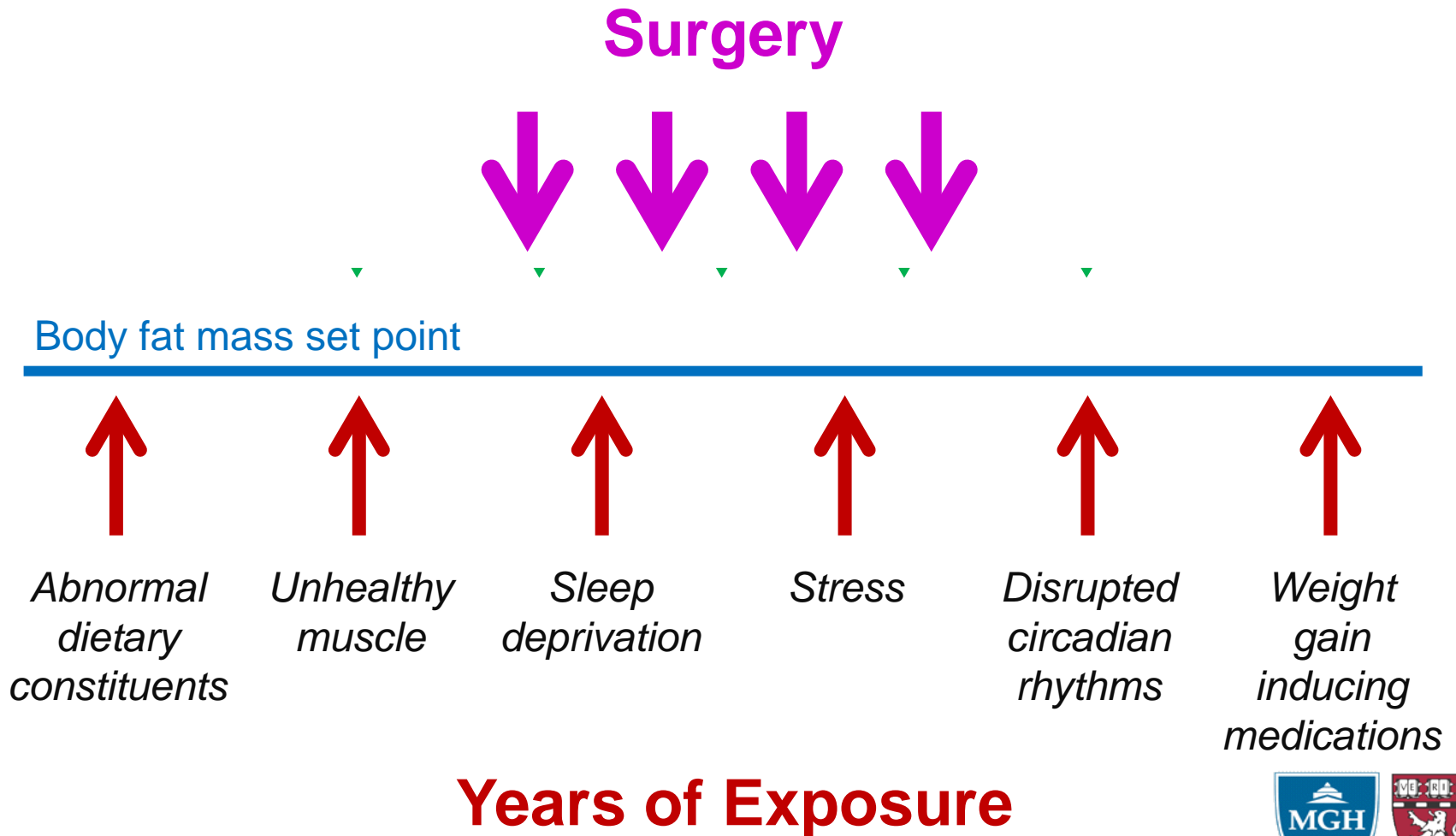


Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

Medications



Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

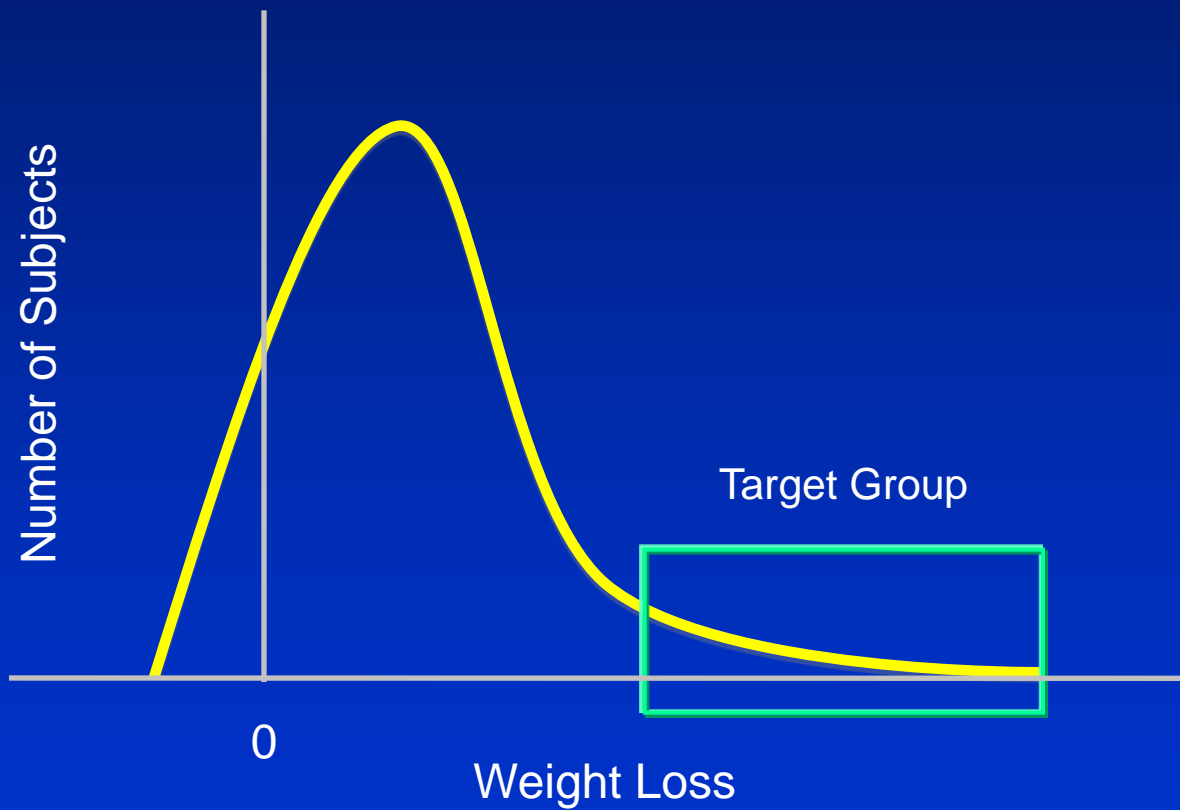


What Differs Among Different Obesity Subtypes

- Timing of obesity onset
- Fat location and distribution
- Metabolic consequences
- Phenotypic differences
 - Hunger
 - Satiety
 - Reward-based eating
 - Energy expenditure
- Response to environmental causes
 - Eating
 - Exercise
 - Stress
 - Sleep deprivation
 - Circadian disruption
- **Response to therapies**



Heterogeneity of Response



Obesity Treatment Strategy

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Self-directed Lifestyle Change

Obesity Treatment Strategy

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Professionally-directed Lifestyle Change

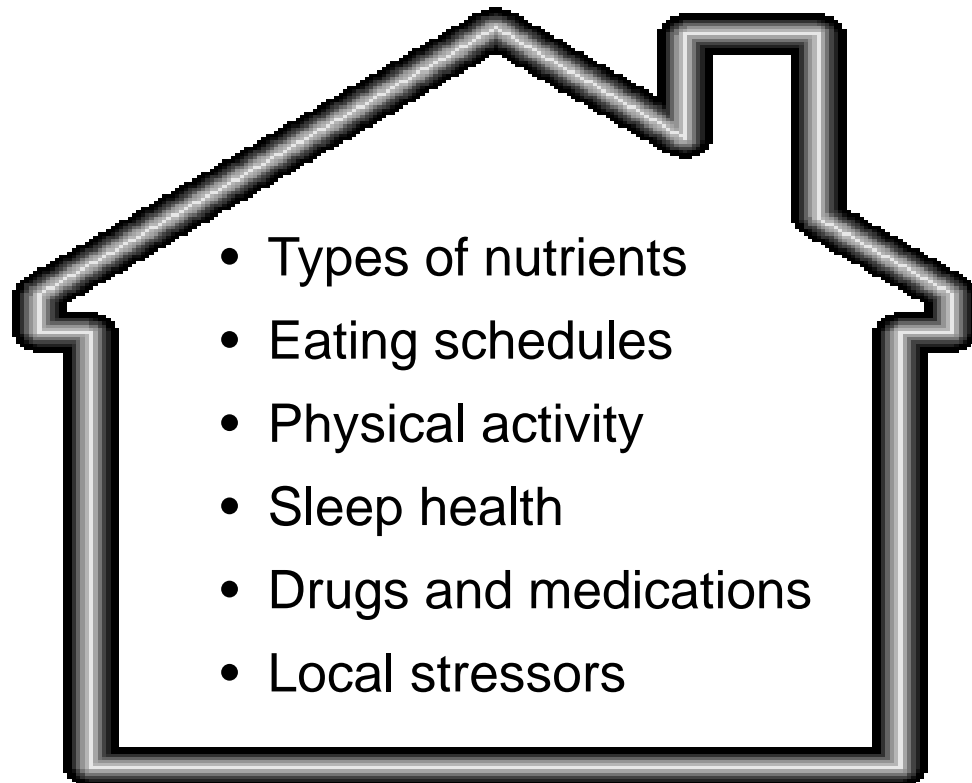
Self-directed Lifestyle Change

Lifestyle Treatment of the Patient with Obesity

- Goal: To reverse the elevated fat mass set point, which is the cause of obesity in the first place
- **Healthy diet – to change nutrient *environment* by changing *chemistry***
 - Improves nutrient signaling to the brain
 - Emphasize unprocessed foods
 - Encourage complexity
 - Number of calories is MUCH less important
- **Regular exercise**
 - To improve muscle health, not to burn calories acutely
 - Long-term exercise more important than type or intensity
- **Stress reduction**
 - Reduce both perceived and “invisible” stresses
 - Restore sleep
 - Regularize circadian rhythms

Goal of Lifestyle Therapy

Normalize the Microenvironment



Patient Self-assessment

- Weight-influencing medications
- Diet content
- Eating patterns
- Sleep health
- Daily physical activity
- Local stressors

Medication-induced Weight Gain

Medications account for 5-10% of obesity in the U.S.

In each relevant category, remove or substitute weight gain-promoting medications with weight neutral or weight loss-promoting alternatives



Weight Loss from Other Medications

Strategy: Aim for Double Benefits when Possible

Medication	Indicated Uses	Comments
Bupropion	Depression	Avoid in bipolar disease
Topiramate	Seizures Migraines Mood disorders	May produce neurological side effects
Zonisamide	Seizures Mood disorders	Few studies
Metformin	Type 2 diabetes PCOS	Rare liver toxicity
Liraglutide. Exenatide	Type 2 diabetes	Injectable
Pramlintide	Type 2 diabetes	Injectable; nausea common
Canagliflozin	Type 2 diabetes	

Lifestyle Strategy

- Keep the goal in mind: **significant** and **durable** weight loss
- **Assess patient's current lifestyle and habits**
 - Identify greatest opportunities for lifestyle change
 - Focus on changes that influence the obesogenic environment, *not* the cardiovascular or other risk
- Pursue **sequential application** of *limited* lifestyle changes
 - Determine effectiveness of each individual change
 - Include non-diet, non-exercise interventions (sleep, stress, circadian)
 - Use classic strategies of habit change (opportunity, cue, reinforcement)
 - Anticipate need for the additive effects of multiple lifestyle changes
- **Aim for clinically significant weight loss**
 - Be in sync with the patient



Obesity Treatment Strategy

Stepwise Approach

(progress through algorithm as clinically required)

Pharmacotherapy

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Self-directed Lifestyle Change

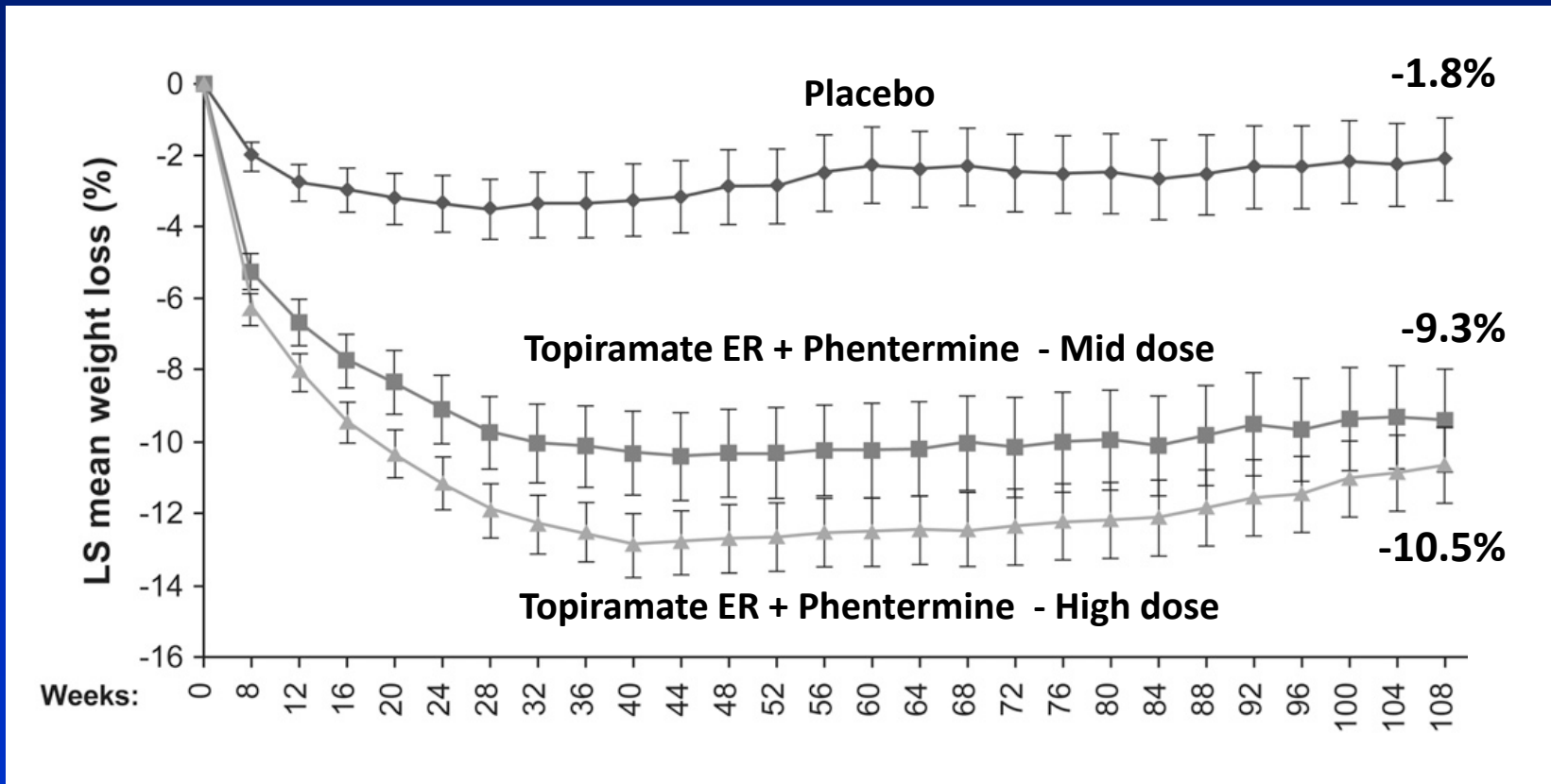
Medications Approved for Obesity - 2015

Medication	Average Weight Loss*	Mechanism of Action	Potential Side Effects
Phentermine (Adipex™, Ionamin™)	~ 5%	Adrenergic	Tachycardia, hypertension
Phentermine / Topiramate (Qsymia™)	10%	Adrenergic, CNS	Tachycardia, hypertension, cognitive dysfunction, neuropathy, teratogenicity
Bupropion / Naltrexone (Contrave™)	4.5%	CNS; opioid antagonism	Seizures, confusion, anxiety, opiate withdrawal
Lorcaserin (Belviq™)	3.5%	Serotonergic (5HT _{2C})	Headache
Liraglutide (Saxenda™)	7%	GLP-1 agonist	Nausea
Orlistat (Xenical™)	3%	Lipase inhibitor	Steatorrhea, incontinence

* Beyond placebo

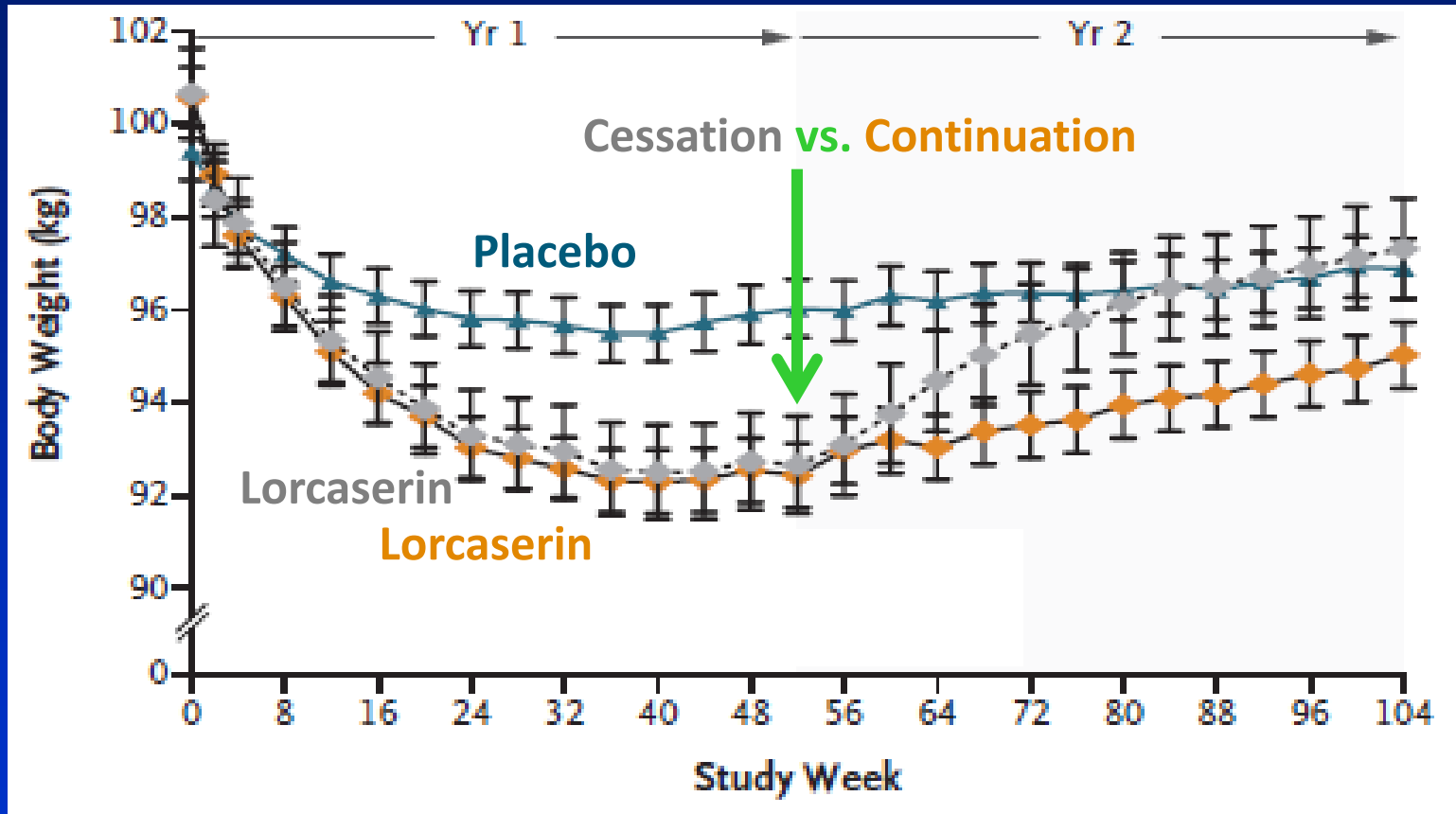
Establishment of a New Plateau (Set Point)

Topiramate ER + Phentermine Combination



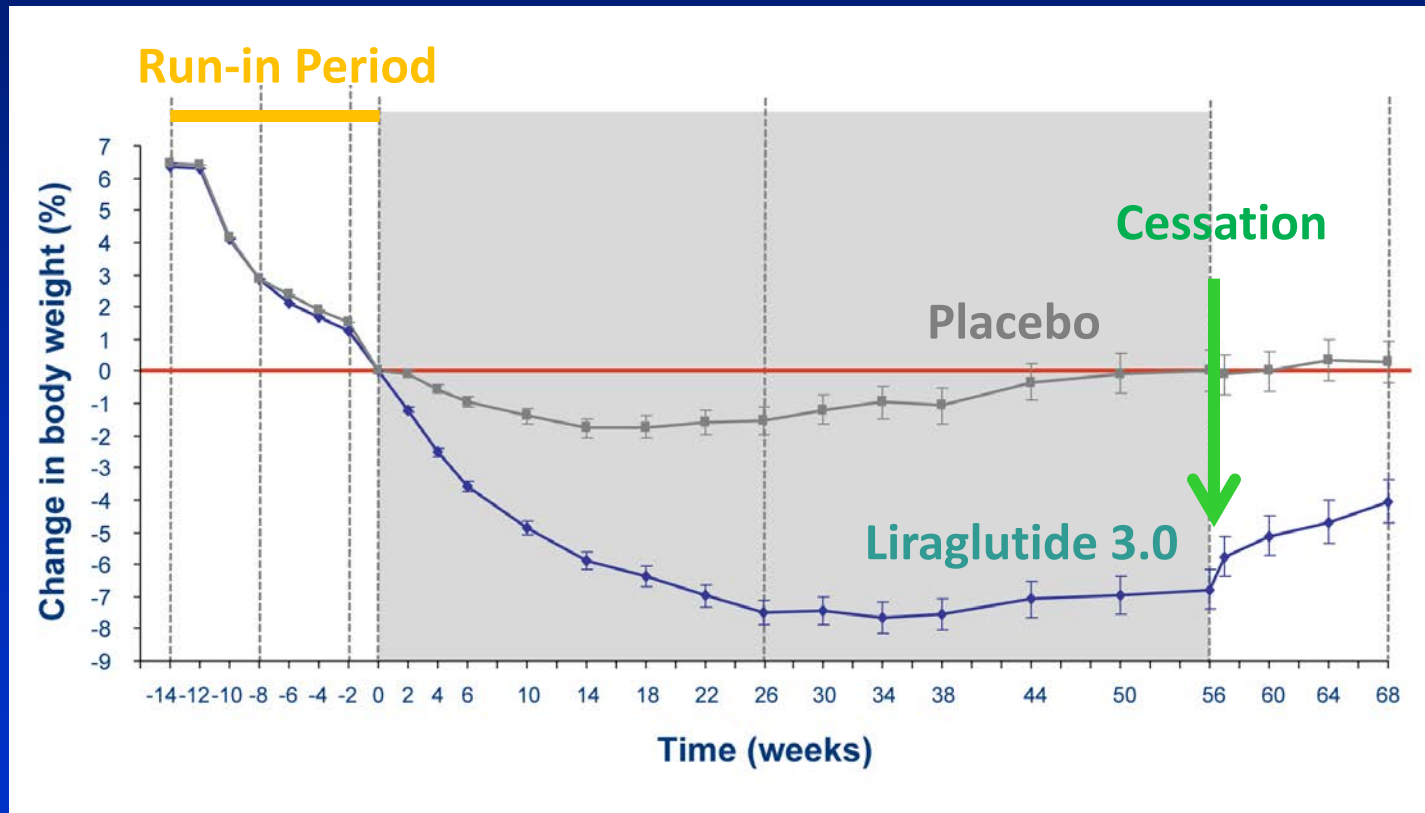
Weight Gain After Treatment Cessation

Lorcaserin



Long-term Weight Maintenance Not Uncommon

Liraglutide



Optimal Pharmacological Strategy

- **Optimize the patient's current medical regimen**
 - Avoid weight gain-promoting medications
 - Substitute a more weight-friendly alternative
- **Personalize the care: find the best treatment for each patient**
 - Pursue sequential trials of different medications
 - Minimum threshold for long-term use: 5% weight loss
 - Build to 2-3 drug combinations as needed
- **Aim for substantial (not merely 5%) weight loss**
- **Use in conjunction with ongoing lifestyle-based therapy**

Choosing an Anti-Obesity Medication

- Response to any single agent is highly variable
- Goal is matching the patient with the most effective agent
- Little or no useful information exists to help predict who will respond to each agent
- Major drivers of which agent(s) to use or avoid:
 - **Specific contraindications**
 - **Predicted risk of adverse events**
 - **Average weight loss**
 - **Patient preference and cost**
- Drugs can be effective in combination that are ineffective alone
- There is a critical need for more effective outcome predictors

Practical Use of Weight Loss Medications

- **Understand risks, cautions and monitoring essentials**
- **Start when weight is stable (within 3% over 3 months)**
 - Aim for weight stability with lifestyle management
- **Assess effects at 1 and 3 months**
 - Continue beyond 3 months if $\geq 5\%$ total weight loss
 - If only modestly effective, may be augmented by addition of a second agent (even one with no solo activity)
- **Weight plateau and return to increased hunger is expected**
 - Medication is still working if no substantial weight regain
- **Anticipate continuing effective regimen indefinitely**

Obesity Treatment Strategy

Stepwise Approach

(progress through algorithm as clinically required)

Weight Loss Surgery

Pharmacotherapy

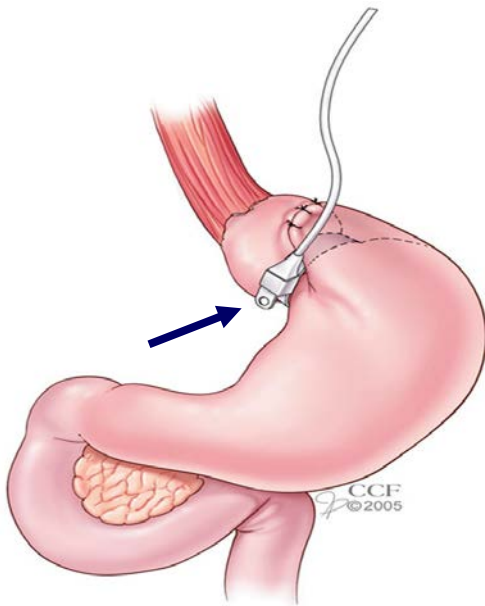
Professionally-directed Lifestyle Change

Self-directed Lifestyle Change

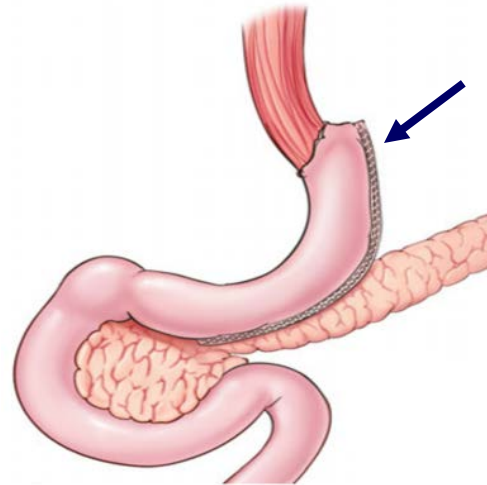
Metabolic Surgery

Weight-independent Metabolic Benefits

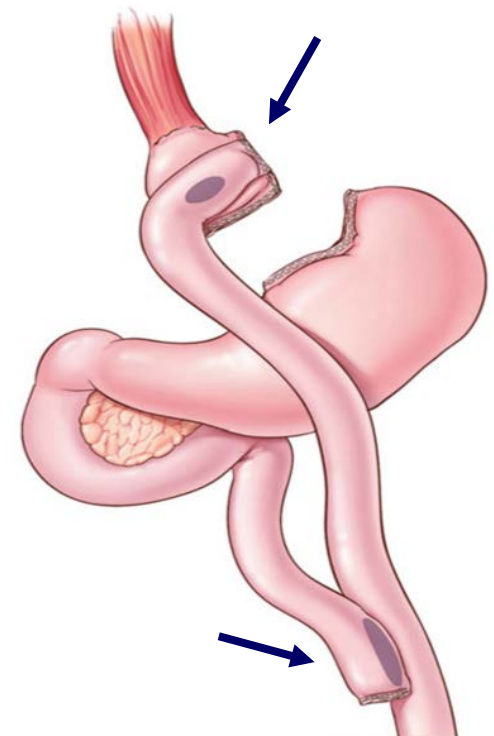
Adjustable
Gastric Banding



Vertical Sleeve
Gastrectomy



Roux-en-Y
Gastric Bypass

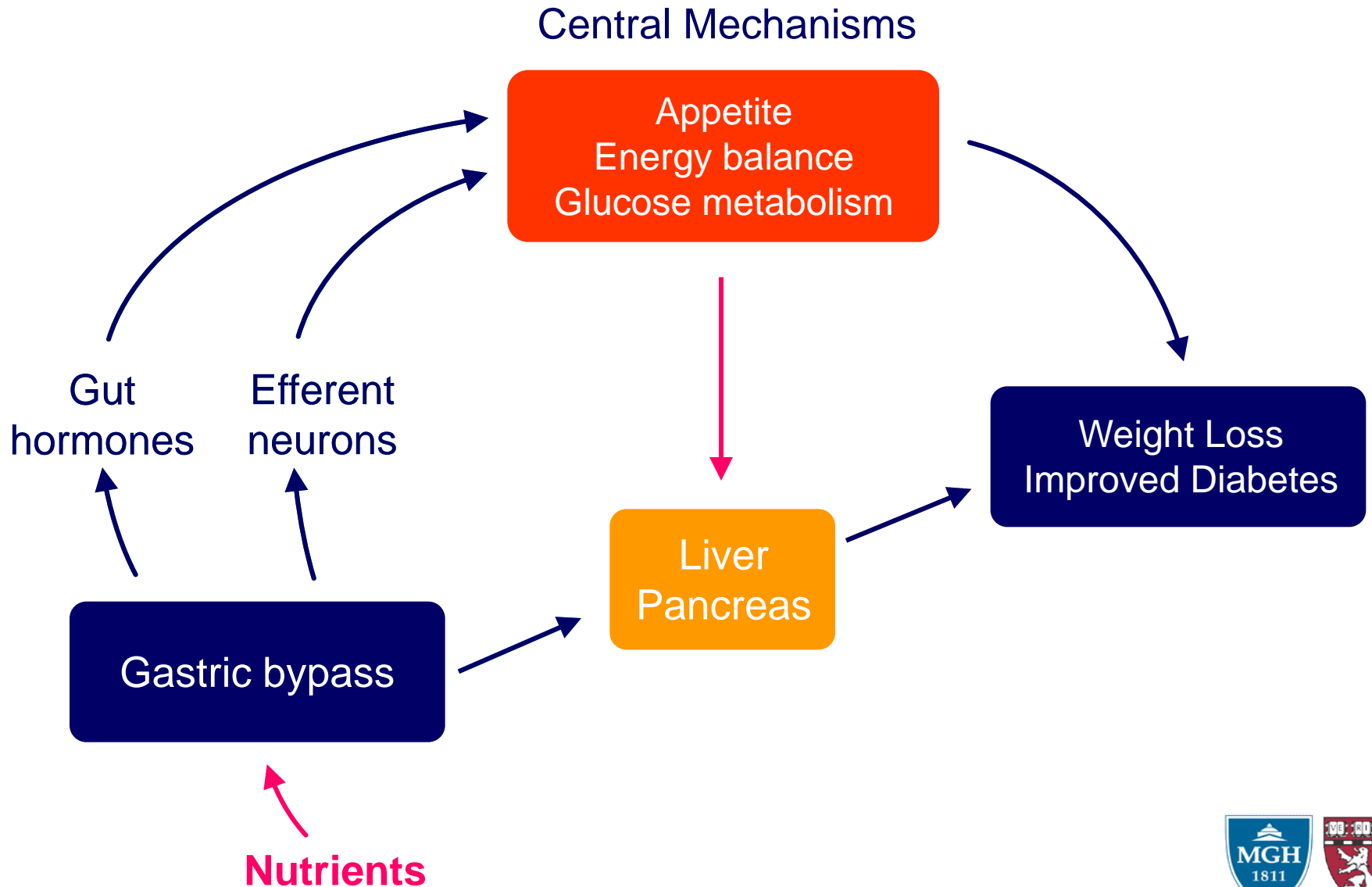


The Physiological Nature of Surgery

- Bariatric surgery is a primarily **physiological**, or **chemical** intervention; effective devices will share these characteristics
 - Both weight loss and improved metabolic function result from these chemical responses
- **Physics** plays a **minimal** role, far less than has been thought in the past
 - **Restriction** may play a significant role in **gastric banding**
 - It is unlikely to contribute significantly to other procedures
 - **Malabsorption** can occur with BPD/DS, but even with this procedure, it is not a primary cause of weight loss or improved metabolic function
- These observations have **critical** implications for the most effective use of these procedures and devices

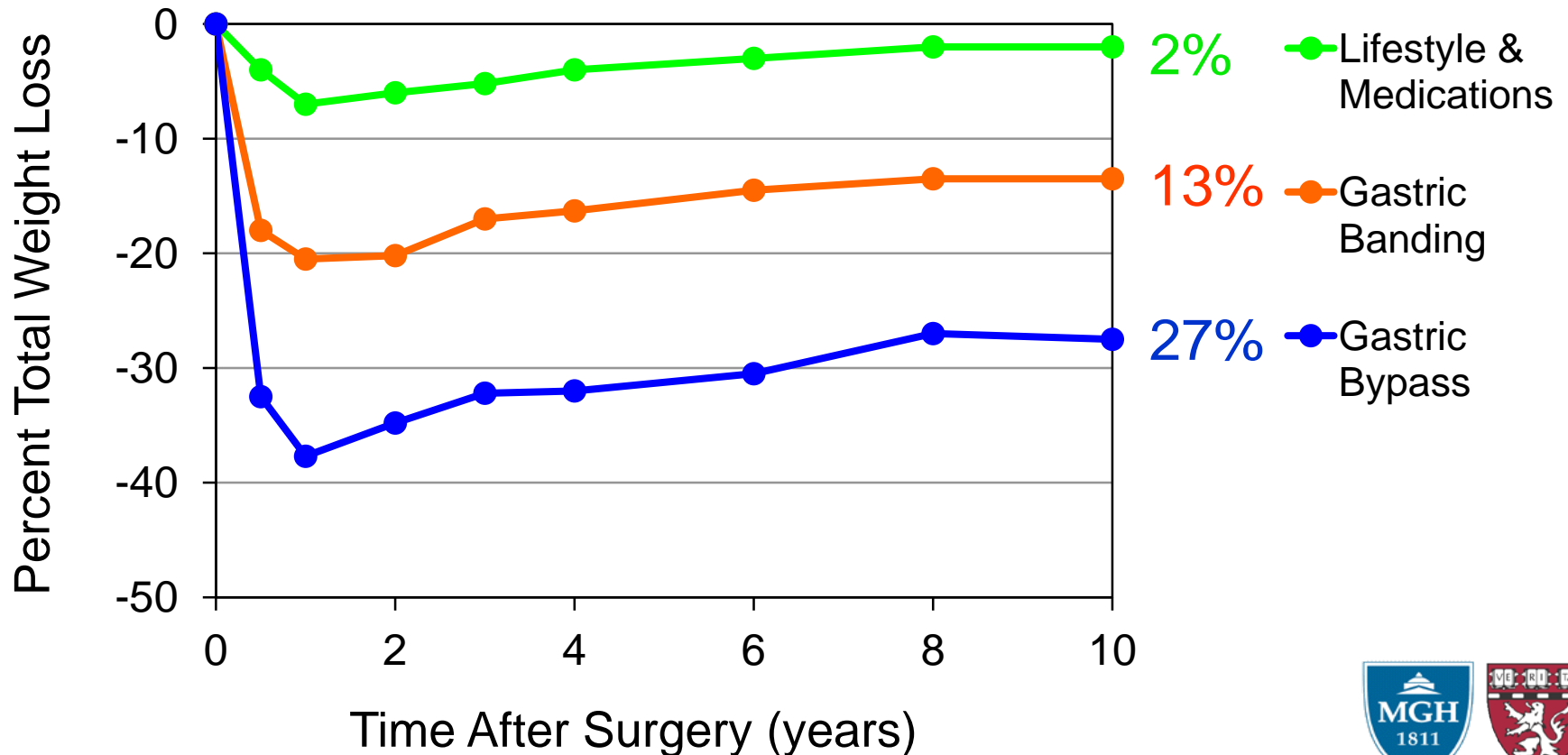


GI Regulation of Metabolic Function



Average Effectiveness of Obesity Treatments

Swedish Obesity Subjects Diabetes Prevention Program



Surgery Decreases Long-term Mortality

Utah Study

- 15850 gastric bypass patients and matched controls
- 7.1 year mean follow-up
- Gastric bypass group exhibited overall 40% reduction in mortality
- Specific-cause mortality after gastric bypass
 - 56% reduction from CAD
 - 92% reduction from type 2 diabetes
 - 60% reduction from cancer



Summary – Bariatric and Metabolic Surgery

- Surgery causes profound and durable weight loss and improvement in diabetes, with frequent complete remission
- Recent data indicate that **early** effects on diabetes result from decreased food intake and weight loss (not specific to surgery)
- The **long-term** benefits are those unique to the biology of surgery
- DM recurrence after complete remission is common, but residual diabetes generally much improved over pre-operative state
- Different procedures work through distinct mechanisms
- **Sleeve gastrectomy** appears about 80% as effective as gastric bypass – for both obesity and diabetes
- **Gastric banding** is much less effective than other procedures, with a much less profound physiological effect
- **Duodenal switch** and **biliopancreatic diversion** are more effective, but whether the added benefit is worth the added risk is not clear

Why is bariatric surgery so effective?



Mechanisms of Bariatric Surgery

Classical model:

Mechanical

Restricted food intake

Malabsorption

Current model:

Physiological

Altered GI signals to brain

- Endocrine
- Neuronal

Altered GI signals to other tissues (pancreas, liver)



Bariatric Surgery

Clinical Evidence for Physiological Mechanisms

1. Dramatic effects on hunger and satiety
2. Few patients become underweight after surgery
3. Transient weight gain during pregnancy
4. Little or no weight loss in thin patients or animals



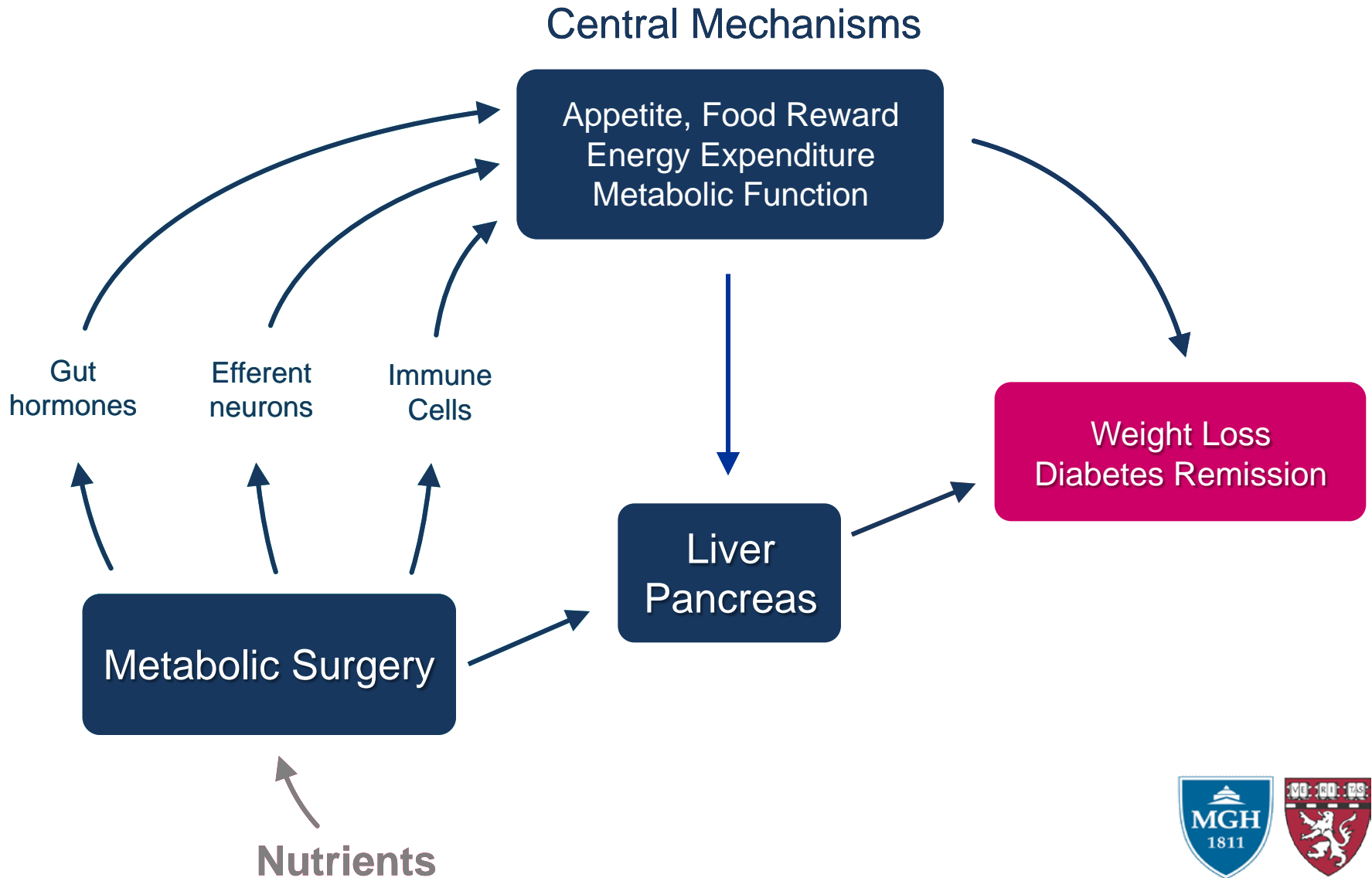
The effects of bariatric surgery are fundamentally
and broadly different from the effects of other
types of weight loss



RYGB is the Opposite of Restrictive Dieting

	Diet	RYGB
Energy expenditure	↓	↑
Appetite	↑	↓
Hunger	↑	↓
Satiety	↓	↑
Reward-based eating	↑	↓
Stress response	↑	↓
Gut peptides		
Ghrelin	↑	↓
GLP-1, PYY, CCK, amylin	↓	↑

GI Regulation of Metabolic Function **After Surgery**



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Post-surgical Combinations

Weight Loss Surgery

Pharmacotherapy

Professionally-directed Lifestyle Change

Self-directed Lifestyle Change

Case Study – A.G.

- 51-year-old woman with BMI 43.3
- Weight 252 lbs., height 5'4"
- Well-controlled hypertension, hypothyroidism, Barrett's esophagus, osteoarthritis (s/p knee replacement), colonic polyps, and depression
- Uncomplicated type 2 diabetes on pioglitazone, glimepiride and insulin (long- and short-acting to total of 65 units/day)
- Sleep apnea well-controlled on CPAP
- Other medications include losartan, hydrochlorothiazide, omeprazole, levothyroxine, aspirin and sertraline



Case Study – A.G.

Examination

Central obesity with waist circumference 41 in.

Benign, protuberant abdomen; no signs of chronic liver disease

No signs of peripheral neuropathy

Laboratory studies

Fasting glucose 111

HbA1c 7.1%

AST 43, ALT 51, alkaline phosphatase 120

BUN 32; creatinine 1.2

TSH 5.64



Case Study – A.G.

Weight and lifestyle history

Normal weight as a child; overweight in college and graduate school (weight 150-175; BMI 26-30)

Progressive weight gain in adult life; “insatiable” appetite with frequent cravings and large portions

Numerous unsupervised, supervised and structured diets with variable weight loss (up to 30 lbs.); none maintained

Average weight stable over the past few years; currently at highest lifetime weight

Married with grown children; works as financial planner

Cooks regularly and well, and entertains often

Exercises three times a week with a physical trainer



Obesity Management Summary

- Approach patient in confident, supportive and non-judgmental way
- Determine BMI at each patient visit to assess
- Counsel patients with obesity on the risks of excess weight and the benefits of weight loss
- Identify the medical comorbidities of obesity in each patient
- Pursue a step-wise strategy for weight loss – lifestyle, medications, and surgery as needed – and explore combinations as needed, including combinations across categories
- Help patients maintain weight loss by optimizing the patients lifestyle – healthy diet, regular exercise, adequate sleep, stress reduction



Practical Guidance

Go Slow and Try Different Approaches

- Test therapies sequentially
- Pursue combination therapies – including combinations of specific lifestyle changes with more classical medical approaches
- Be supportive
 - Be persistent
 - Be there for the patient

Aim for the “cure,” but always provide the care.

