Obesity

Patho-physiology and Medical Management

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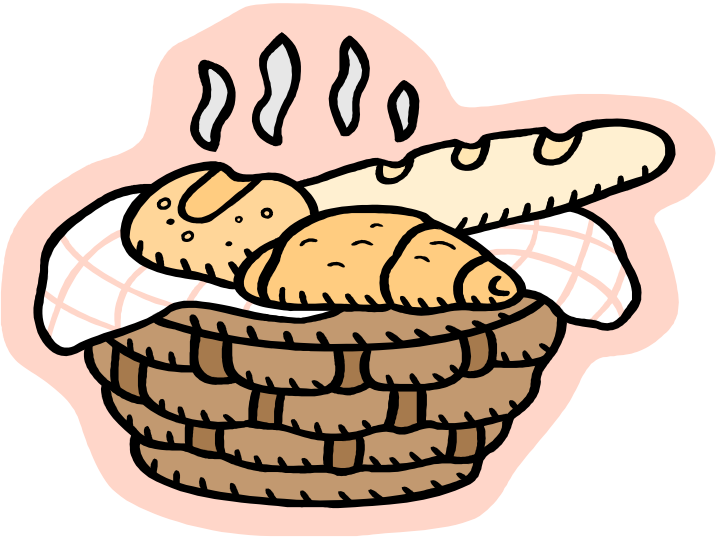
Normal Physiology of Appetite & Satiety

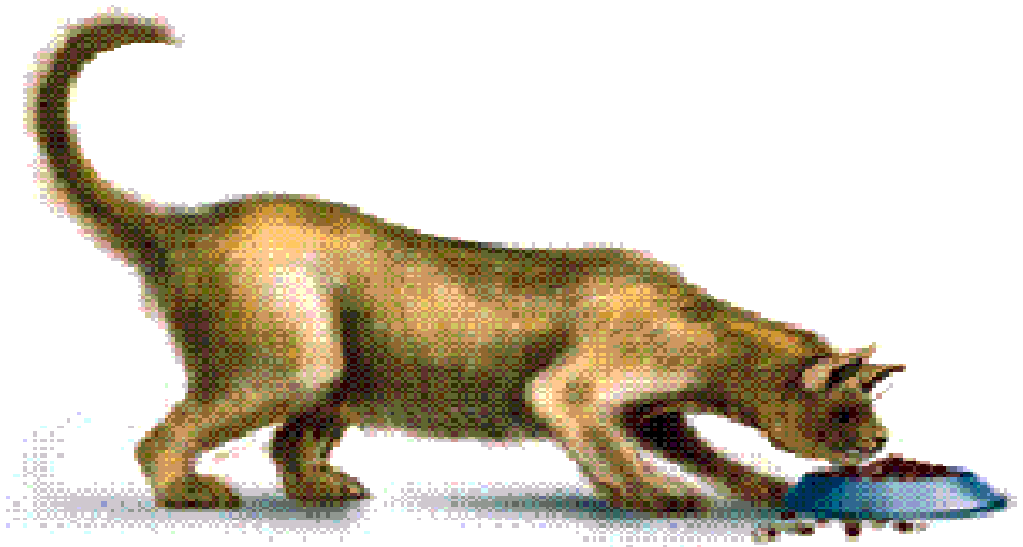


complex interaction of multiple **brain centers**,

hormones, and **sensory** and **motor** pathways

Hunger center

a region in the *lateral hypothalamus* that triggers the desire for food



stimulated

destroyed

Satiety center

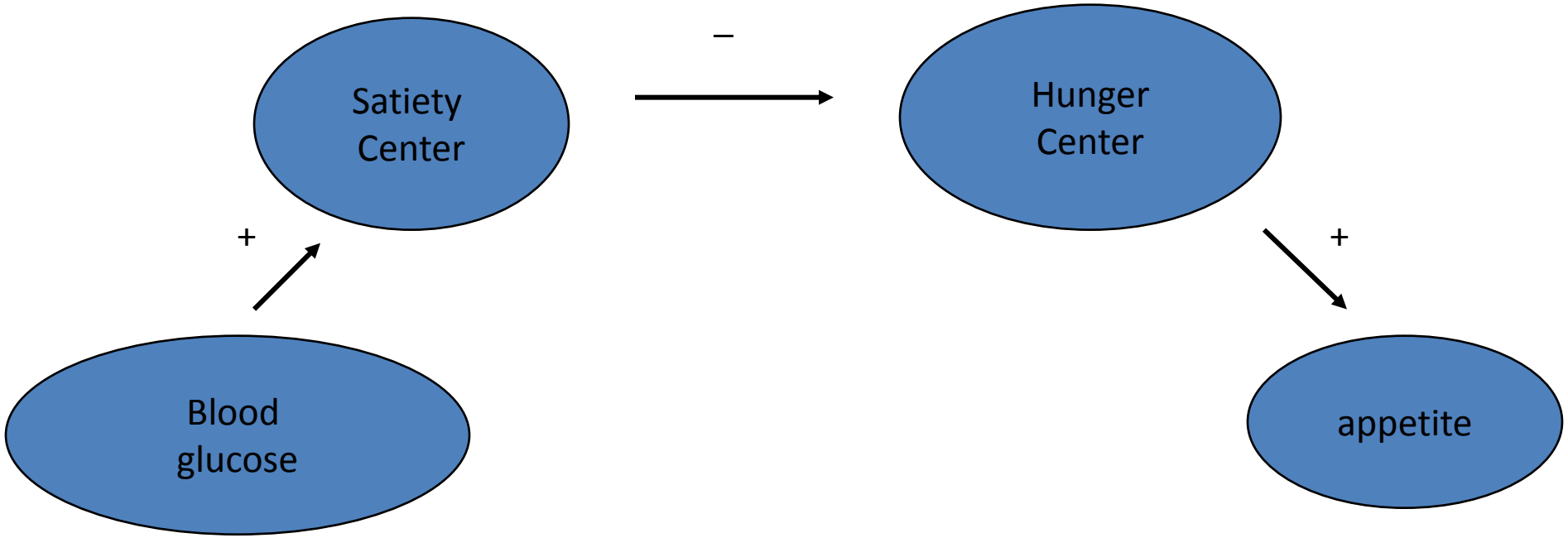
a region in the ***ventromedial hypothalamus*** that suppresses the desire for food

stimulated

destroyed

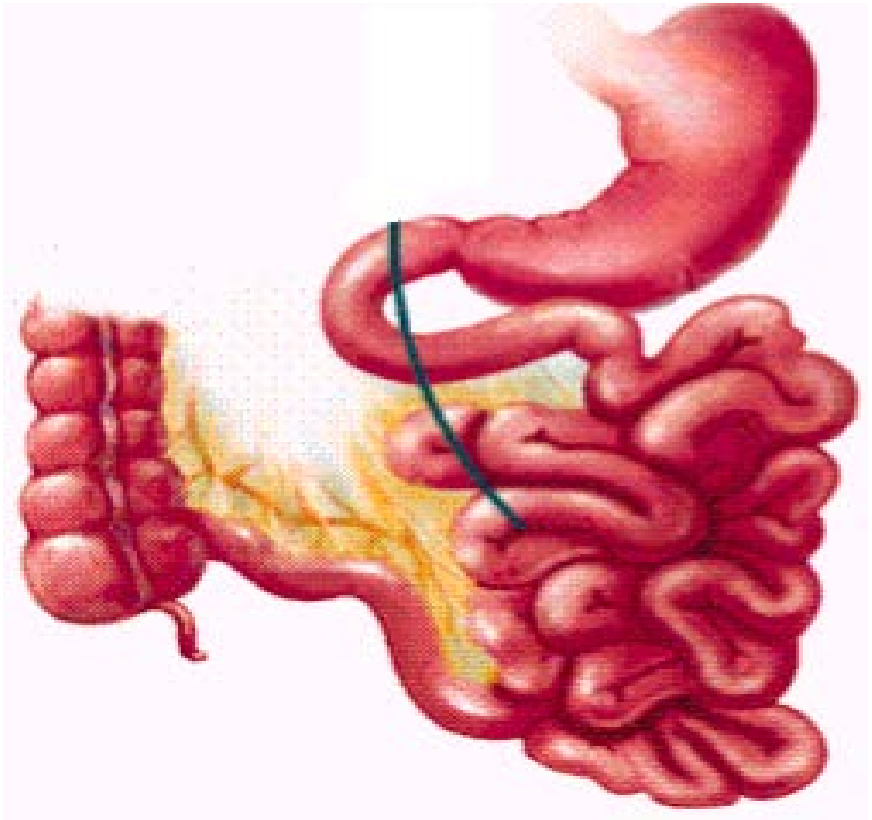
The satiety center has neurons called ***glucostats*** that rapidly absorb blood glucose after a meal.

hypothesis: glucose uptake causes the satiety center to send inhibitory signals to the hunger center and thus suppresses the appetite.



Gastric peristalsis stimulates hunger.

Mild hunger contractions begin soon after the stomach is emptied and increase in intensity over a period of hours.



Role of Hormones in Appetite Regulation

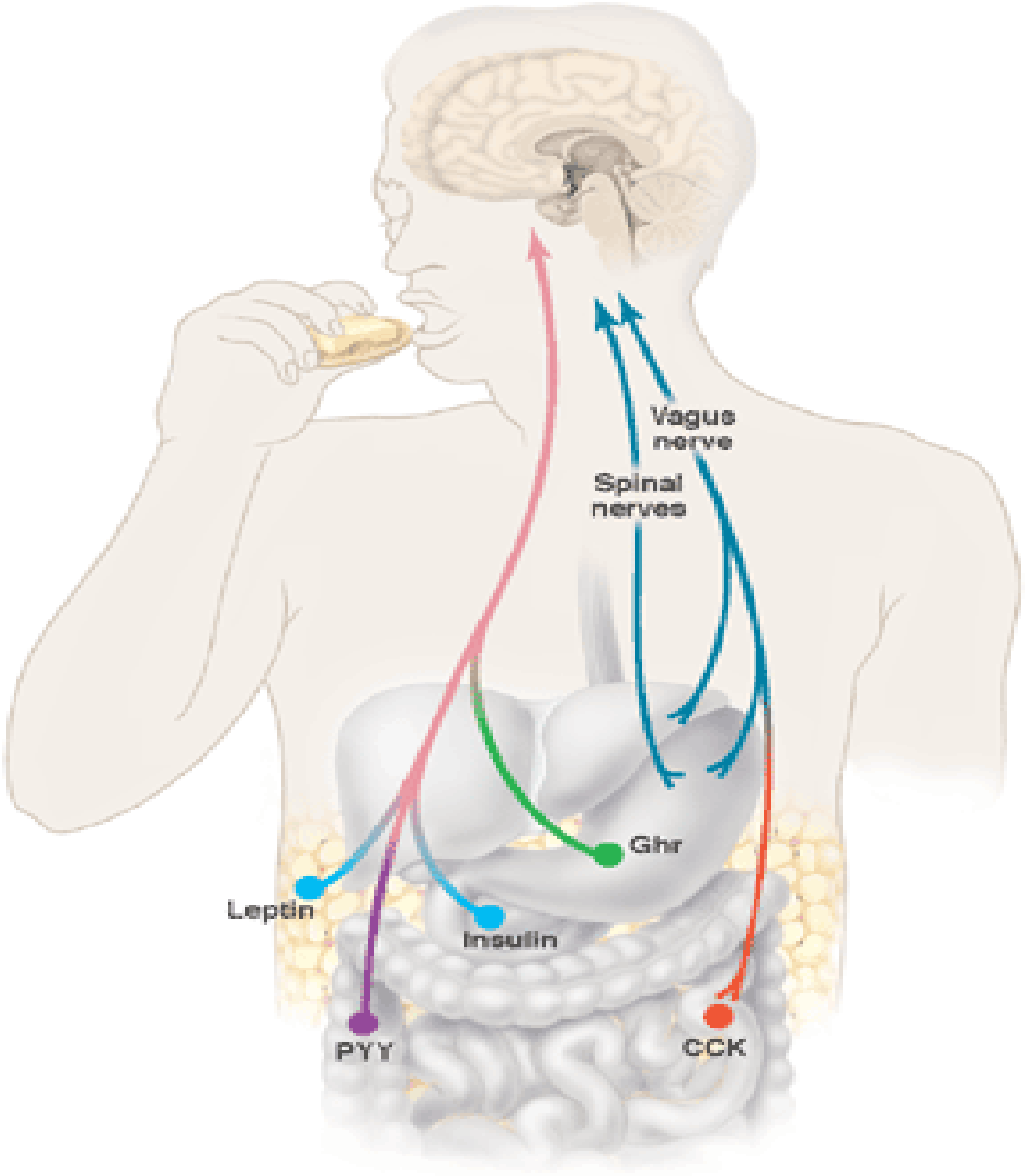
- Hormones from GI: cholecystokinin:

suppressant

ghrelin: stimulant

PYY: suppressant

- Adipocytes (fat cells) secrete hormones (leptin) that regulate appetite and body weight.



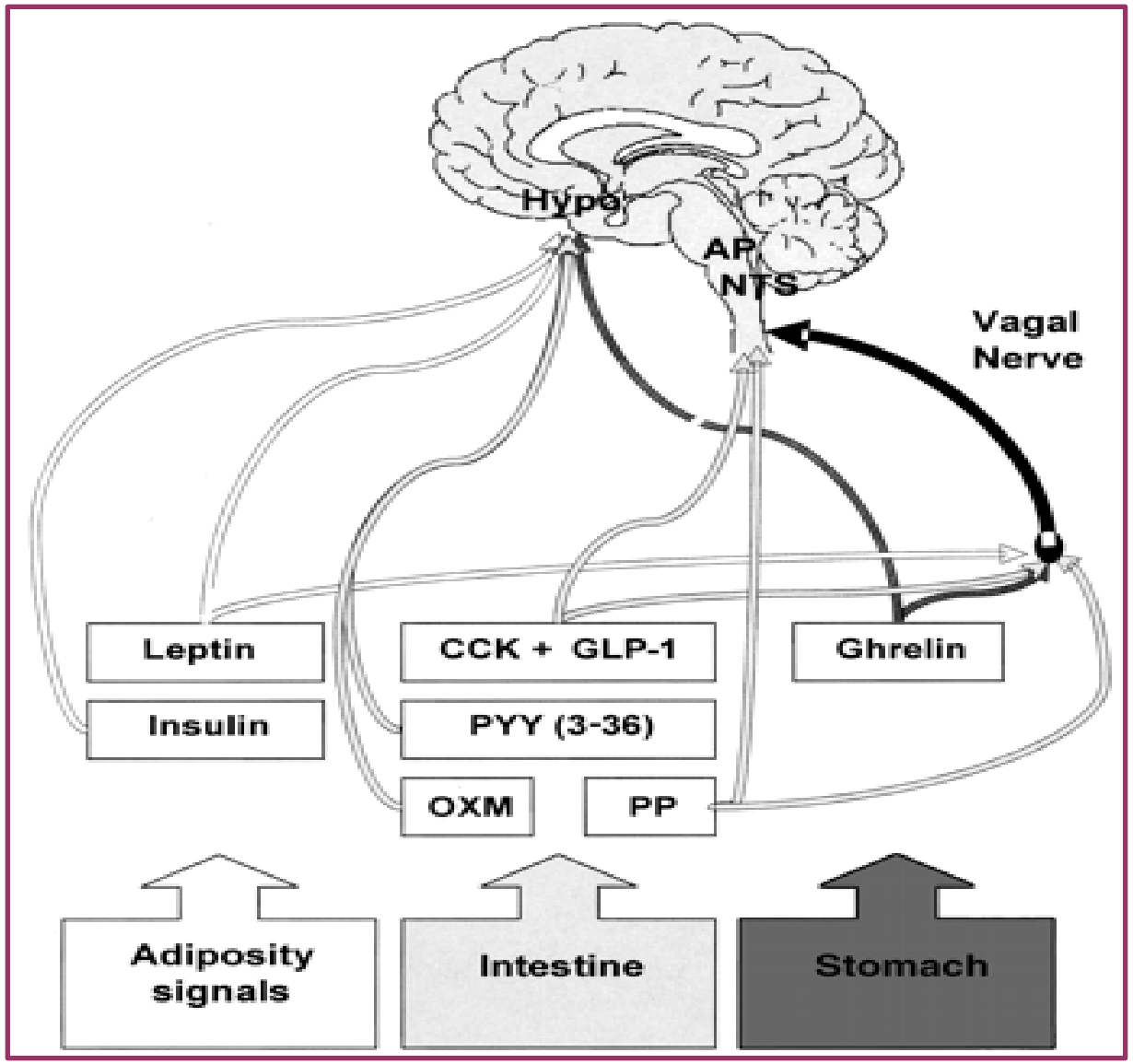
(Science 299:846-849 2003)

Peptides, Hormones & Neurotransmitters

Effect On Eating

Orexigenic	Anorectic
Neuropeptide Y (Y_1)	Serotonin
GABA (A)	Cholecystokinin
Norepinephrine (α_2)	Dopamine (D_2)
Glucocorticoid (type II)	Leptin
Galanin	Insulin
Opiods	TRH
Aldosterone (type I)	Calcitonin
Opiods	Bombesin
GHRH	VIP
Ghrelin	CRH
	Neurotensin
	CGRP
	Glucagon
	IL-1 and 2
	TNF, Prostaglandin

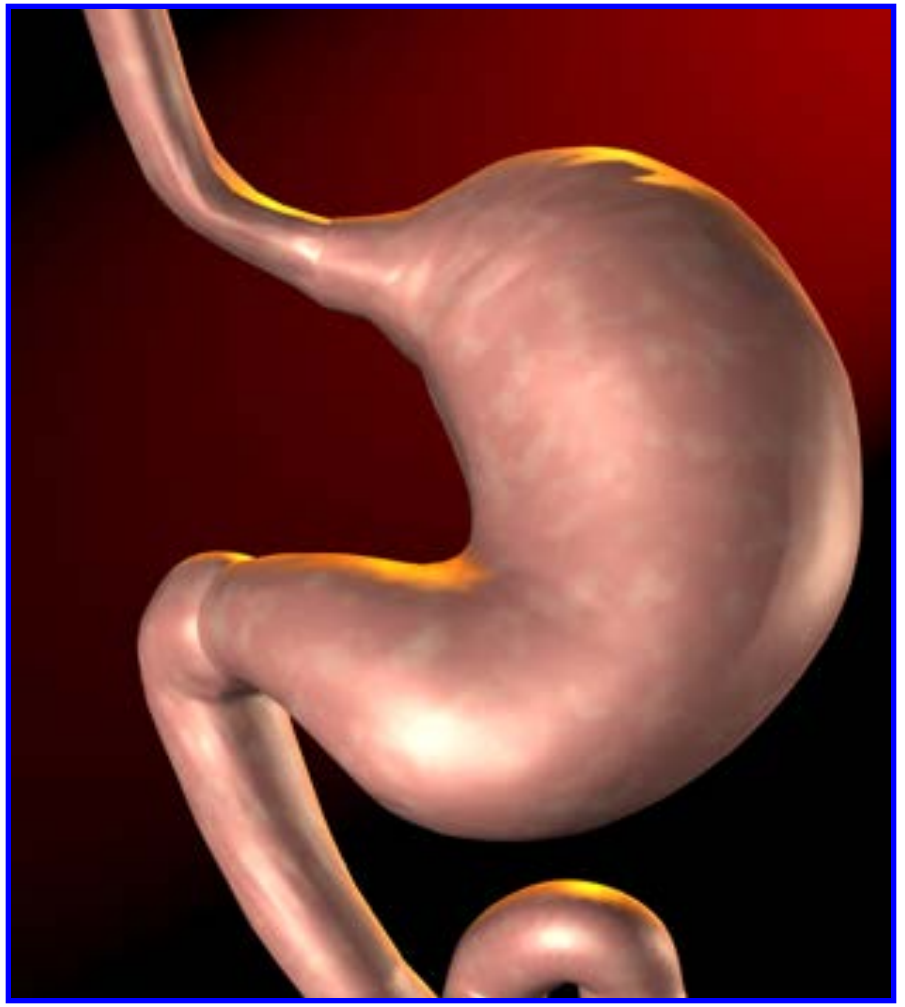
Appetite Control



Wynne et. al., JCEM 2004, 89(6):2576-2582

Gastro-Intestinal Regulation of Appetite

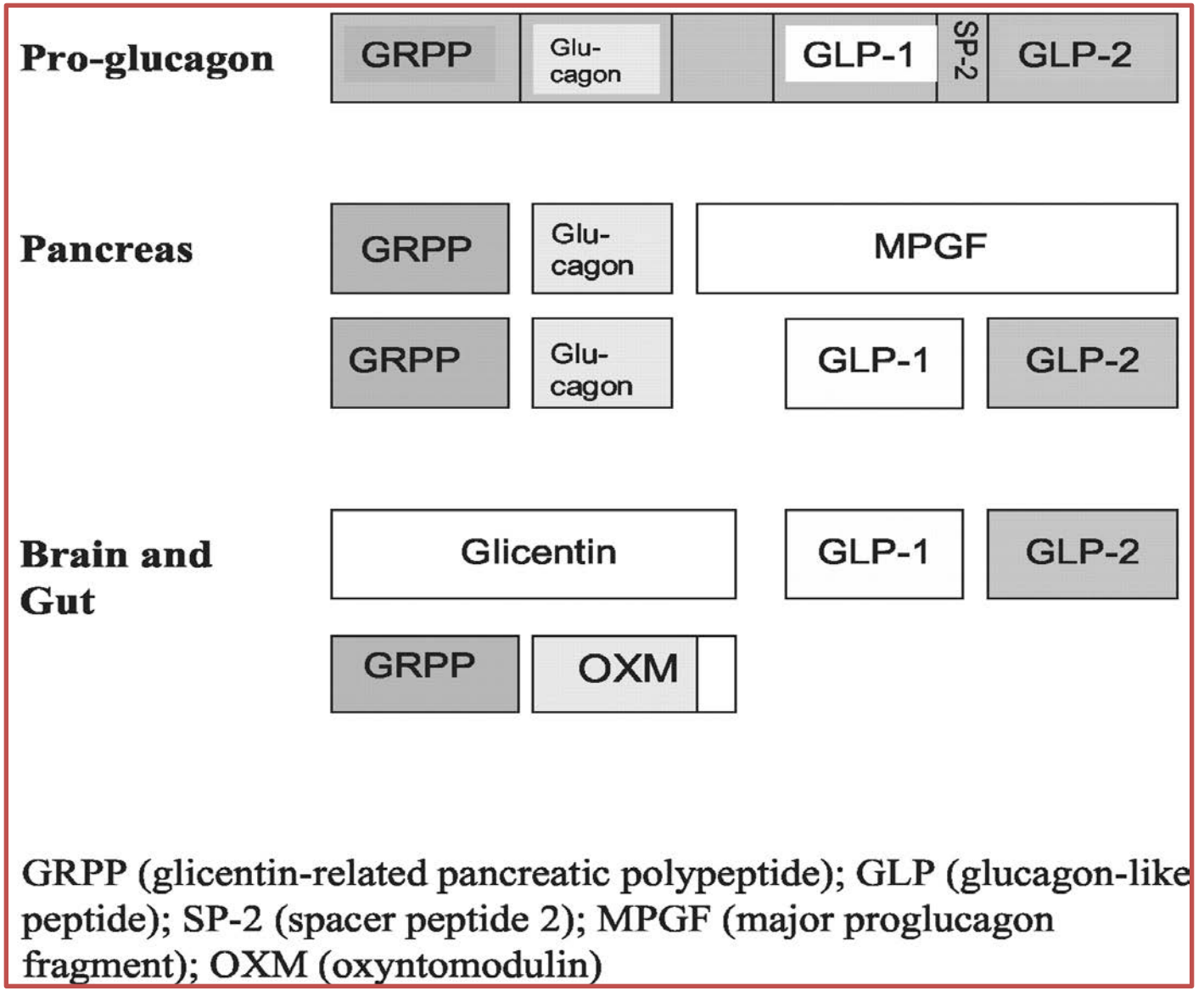
- Ghrelin
  - Secreted from oxyntic cells of stomach
  - Initiates hunger
    - Increases before meal
    - Decreases afterward
  - Increases calorie intake
- True role in decreasing appetite is debated



Intestinal Regulation of Appetite

- Peptide YY (PYY)
  - Satiety and nutrient absorption
  - Crosses blood brain barrier
  - Secreted from entire intestine
    - Greater in distal
    - L cells
  - Stimulated by food via vagal stimulation
  - Increased levels
    - High calorie
    - Fat
- Inactivated by dipeptidyl peptidase IV (DPPIV)
- Pancreatic polypeptide (PP)
  - Satiety and nutrient absorption
  - Produced by pancreas
    - Colon and rectum
  - Stimulated by food
  - More is released with later meals of the day
- Increased with anorexia
- Variable levels seen with obesity

Intestinal Regulation of Appetite



GRPP (glicentin-related pancreatic polypeptide); GLP (glucagon-like peptide); SP-2 (spacer peptide 2); MPGF (major proglucagon fragment); OXM (oxyntomodulin)

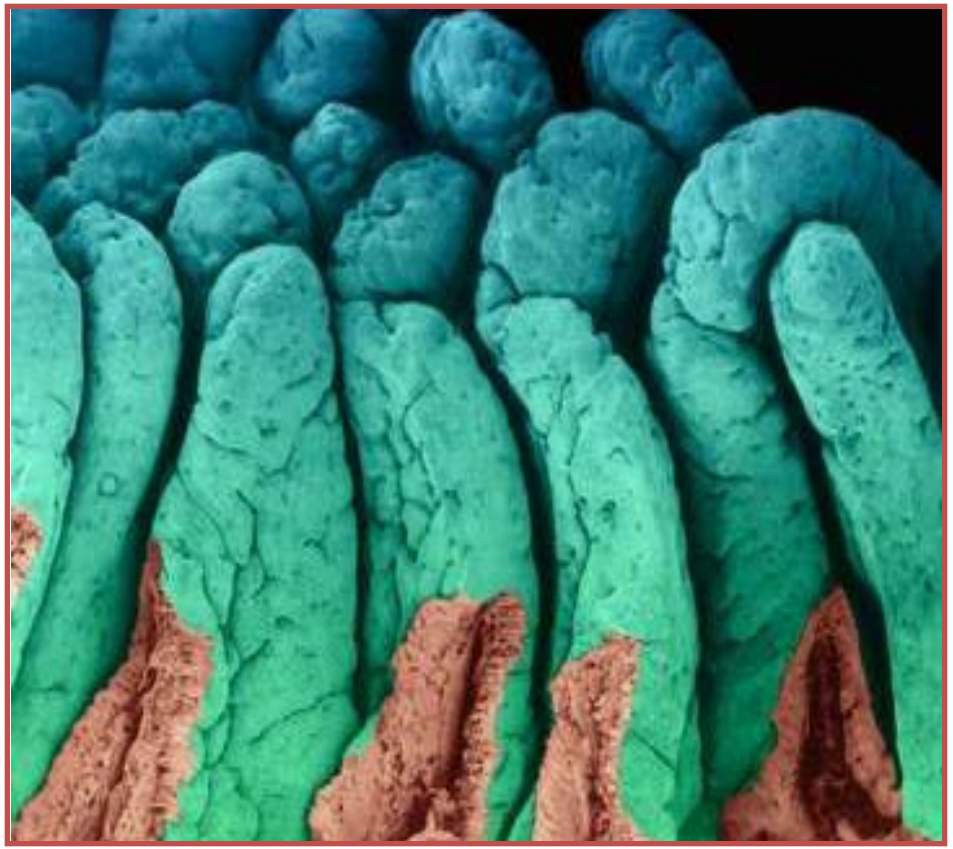
Wynne et. al., JCEM 2004, 89(6):2576-2582

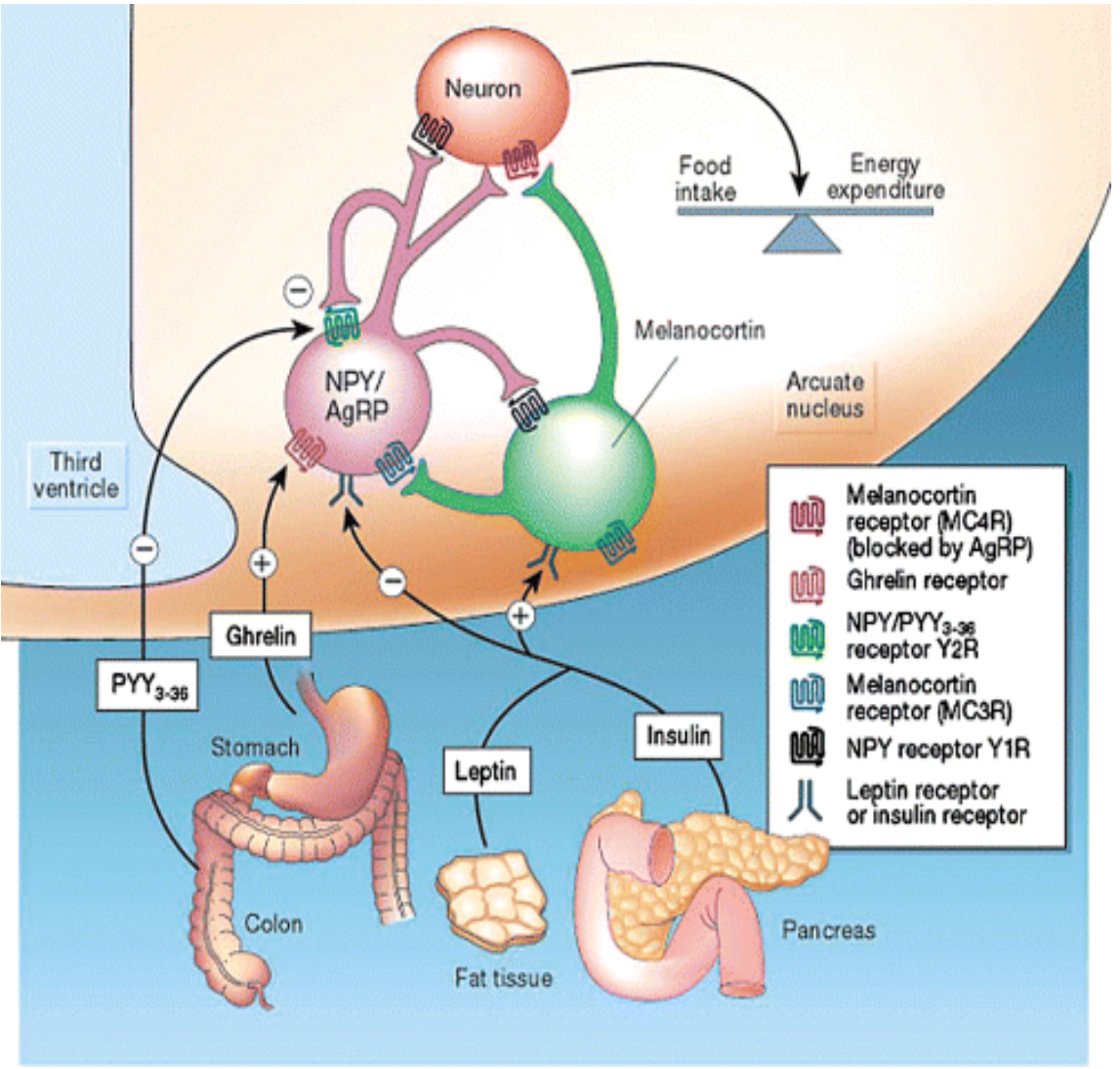
Intestinal Regulation of Appetite

- Glucagon-like peptides (GLP-1 & 2)
  - Satiety
  - Expressed in brain, pancreas and small intestine
    - L-cells
  - Stimulated by food
  - Acts via the GLP-1 receptor
  - Augments postprandial insulin secretion
  - Decreases gastric motility
  - Inhibits gastric acid secretion
- Oxyntomodulin (OXM)
  - Satiety
  - Expressed in brain, and small intestine
    - L-cells
  - Stimulated by food
  - Acts via the GLP-1 receptor
  - Augments postprandial insulin secretion
  - Decreases gastric motility
  - Inhibits gastric acid secretion
  - Meal termination
    - Inhibits Ghrelin

Intestinal Regulation of Appetite

- Cholecystokinin (CCK)
  - Satiety and nutrient absorption
  - Released by duodenum and jejunum
    - L cells
  - Stimulated by intraluminal food

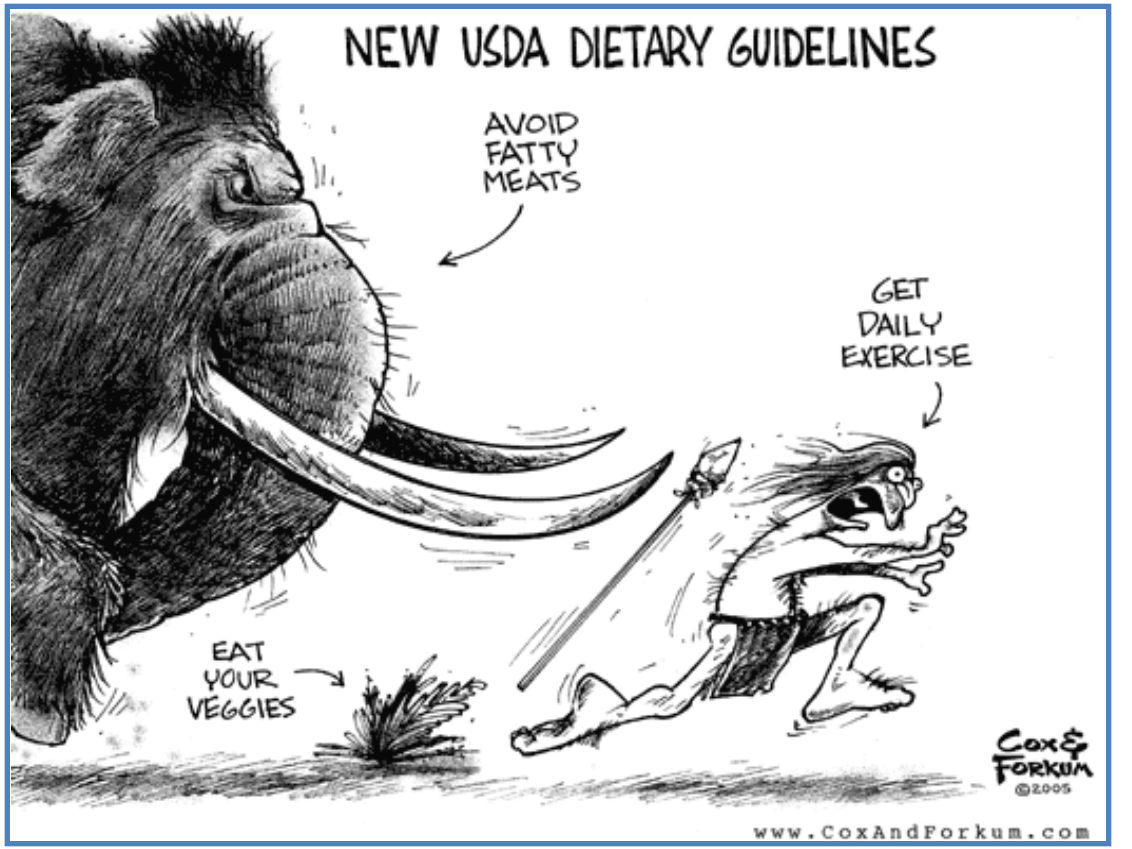




- Leptin and insulin proportionate to body-fat mass.
- Decrease appetite by inhibiting neurons that produce the molecules NPY and AgRP,
- Stimulating melanocortin-producing neurons in the arcuate-nucleus region of the hypothalamus, near the third ventricle of the brain.
- NPY and AgRP stimulate eating, and melanocortins inhibit eating.
- The gastric hormone ghrelin stimulates appetite by activating the NPY/AgRP-expressing neurons.
- PYY released from the colon, inhibits these neurons and thereby decreases appetite for up to 12 hours.

Gastric-bypass
Hormonal Changes

- After bypass
  - Ghrelin variable results
  - Leptin decreases
  - Glucose decreases
  - Insulin decreases
  - Adiponectin increases
  - CCK, VIP and Serotonin unaffected



Post Surgical Changes

- METABOLIC COMPLICATIONS
- Nutritional Deficiencies
- Anemia
- Bone Disease
- Neuropathy
- Vit. A Deficiency
- Vit. D Deficiency

Obesity

- National Institutes of Health :

  Anyone with a body mass index of 30 or above is considered obese. A body mass index above 40 is considered morbidly obese.

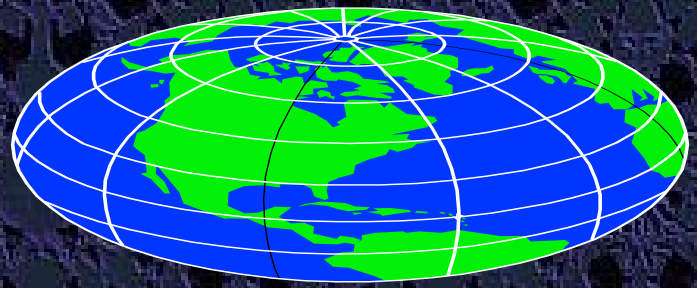
Obesity-Epidemiology

- It is the 2nd most preventable cause of death after smoking
- Decrease life expectancy (2.4 years)
- Increased in co-morbid illnesses

Facts & Figures

- Obesity has surpassed starvation!
- More people are dying due to obesity than starvation

- About 2.2 crore in India



- 33% Americans are affected by obesity

- 1.2 billion obese in the world!

- More than 25% of Indians are overweight
- More than 3% are Obese (3 crores Indians)
- >5% of urban adults are obese
- >15% of urban children are overweight.

WHO classification of obesity

BMI = weight(kg)/height(m)2

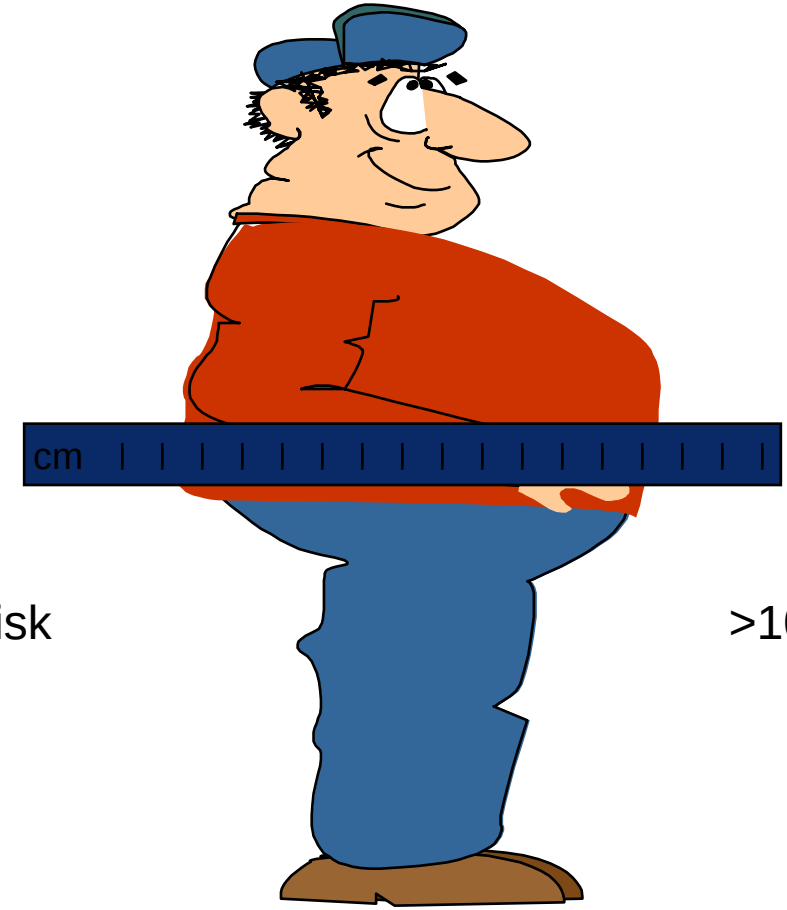
WHO Classification	BMI	Risk of Death
Underweight	Below 18.5	Low
Healthy weight	18.5-24.9	Average
Overweight (grade 1 obesity)	25.0-29.9	Mild increase
Obese (grade 2 obesity)	30.0-39.0	Moderate/severe
Morbid/severe obesity(grade 3)	40.0 and above	Very severe

World Health Organisation. Obesity: Preventing and Managing the Global Epidemic. Geneva: WHO, 1997 [3]

DIAGNOSTIC CRITERIA FOR OBESITY

1. W.H.O. 1999 (Criterion)		
(a) BMI (Adults)	Normal Over Weight Obese	20-25 25-30 > 30 Kg/m^2
(b) Waist Hip Ratio	Normal Male Normal Female	0.90 0.85
2. European Group for the study of Insulin Resistance – 1999		
Waist circumference	Male Female	> 94 cm (37”) > 80 cm((32”)
3. National Cholesterol Education Program Audit Treatment Panel - Guidelines in 2001 Adult		
Central Obesity : Waist circumference		> 102 cm. Male > 88 cm. Female
4. Indian Criteria for Obesity (Indian Institute of Nutrition, Hyderabad)		
BMI	23 – 25 26 – 32 33 – 37 > 37	Overweight Obese Severe obesity Morbid obesity

Body fat distribution
Apple shaped obesity



Women

>88 cm (80cm) = Increased risk

Men

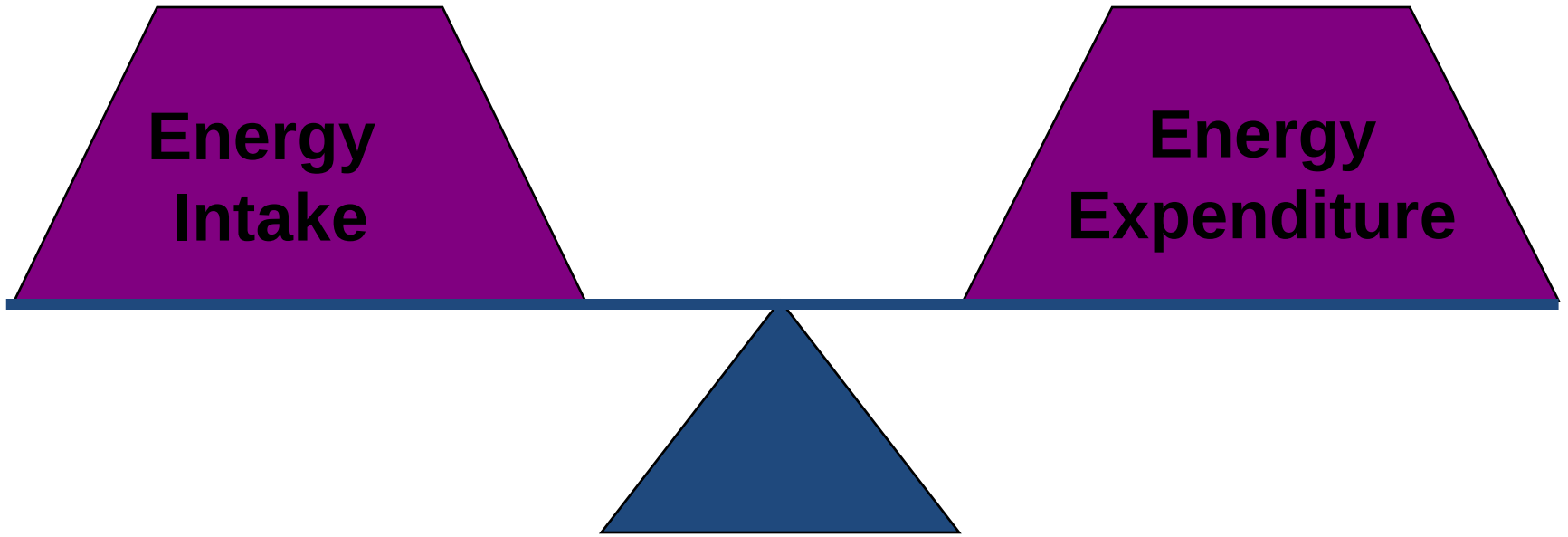
>102 cm (90cm) = Increased risk

Lean MEJ et al. Lancet; 1998; 351:853-6

TYPES

TYPE – I	TYPE – II	TYPE – III	TYPE – IV
General	Android	Visceral	Gynoid
		Android	Gluteal
			Femoral

Causes of Obesity



nutritional, activity levels, endocrine, genetic, drugs

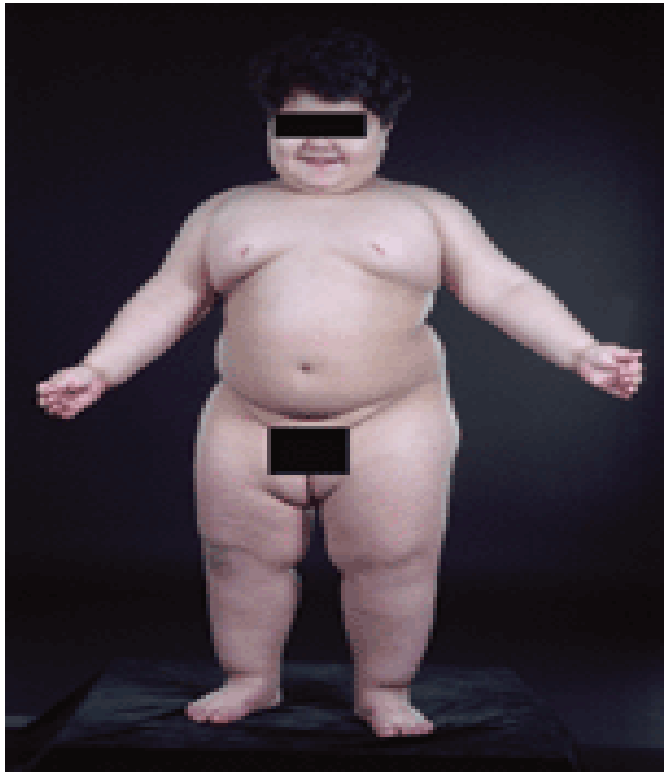
- Genetics
- Environment
- Metabolism
- Eating Disorders and Medical Conditions
- Contributing Factors
- Drugs

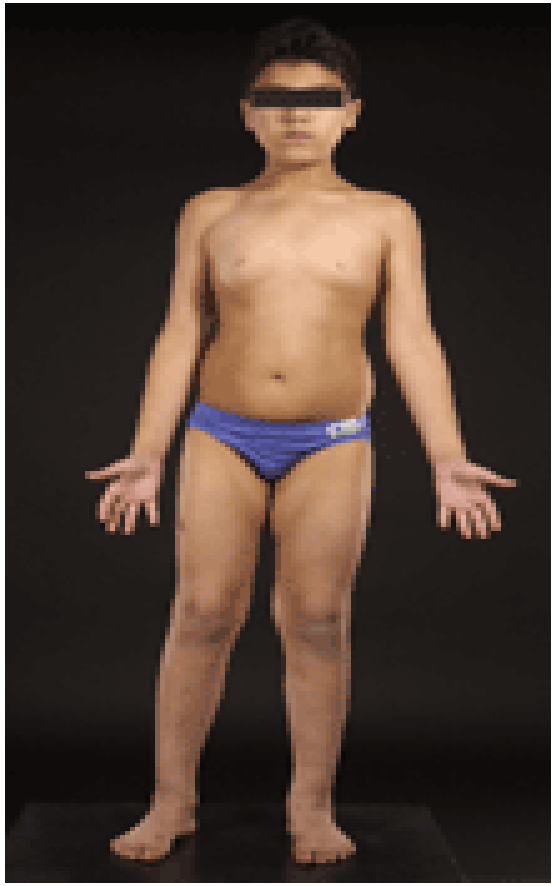
Genetic Causes

- Obese parents
- Monozygotic Twins
- Pima Paradox
- Leptin Deficiency
- Maternal Weight / Breast Feeding / Childhood Obesity

- Agouti gene / Mahogany gene
- Leptin gene
- Leptin Receptor gene
- Prohormone convertase I deficiency (PCSK 1)
- TUB gene
- FTO gene
- PPAR gamma
- BDNF

- Prader Willi syndrome
- Bardet Biedl Syndrome





Leptin's effects. Because of a gene defect, the boy doesn't make leptin, but treatment with the hormone, begun when he was 3.5 years old (*top*), brought his weight down to normal levels, as shown at age 8.

(Science 299:846-849 2003)

Environmental

- Pima Paradox
- Life style
- Sedentary life
- Sleep Deprivation
- Stopping Smoking
- Peers

Endocrinal Causes

- Glucocorticoid excess (Cushing's Syndrome)
- Hypothyroidism
- Growth hormone deficiency
- Hypothalamic dysfunction
- Polycystic ovarian syndrome

Eating Disorders

- Diet Pattern
- Night Eating
- Bizarre Eating
- Fast Food
- Frequency

Drugs

- Antipsychotics
- Antidepressants
- Antiepileptics
- Antidiabetics
- Betablockers
- Cyproheptadine
- Steroids

Other

- Adenovirus Infection
- Ethnicity
- Socioeconomic Group

Lab Studies:

Fasting and 2-hour postglucola glucose and insulin levels and hemoglobin A1c (for evaluation of insulin resistance and glucose tolerance)

Fasting lipid panel for detection of dyslipidemia

Thyroid function tests

Adrenal function tests, when indicated, to assess the possibility of Cushing Syndrome

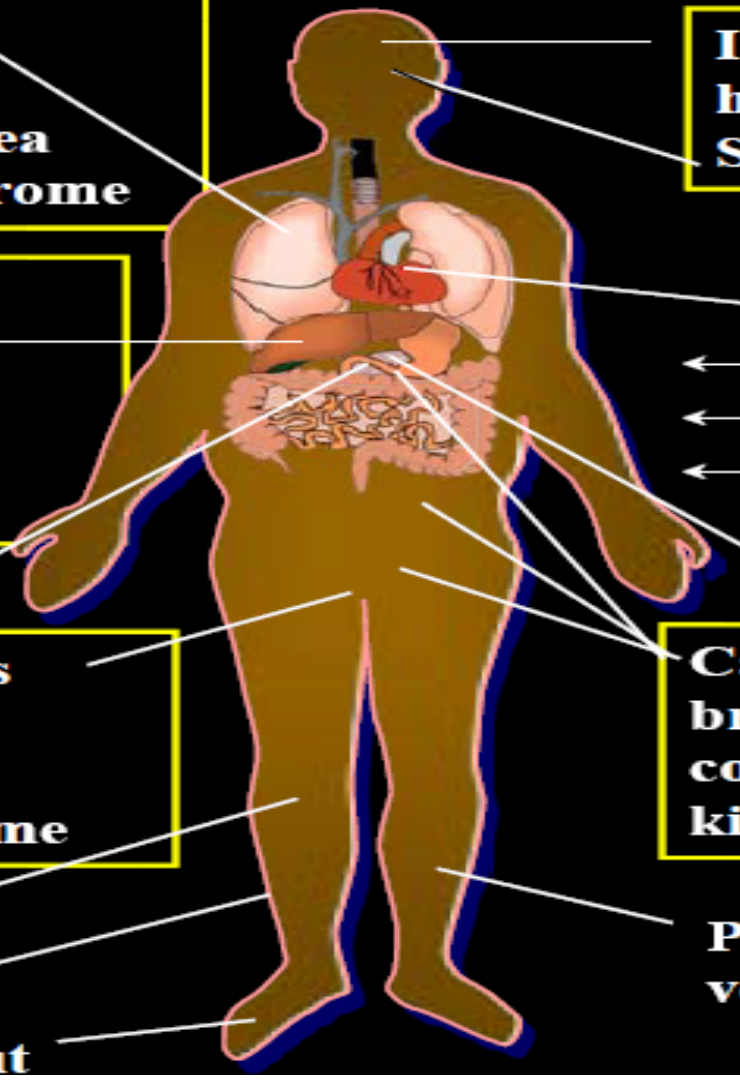
Karyotype when indicated by clinical history and physical examination

Growth hormone (GH) secretion and function tests, when indicated

Assessment of reproductive hormones (including prolactin), when indicated

Serum calcium, phosphorus, and parathyroid hormone levels to evaluate for suspected pseudohypoparathyroidism

Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Idiopathic intracranial hypertension
Stroke

Cataract

Coronary heart disease

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Diabetes
Dyslipidemia
Hypertension

Gall bladder disease

Severe pancreatitis

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Osteoarthritis

Skin

Gout

Phlebitis
venous stasis

Obesity- Associated Co-morbidities

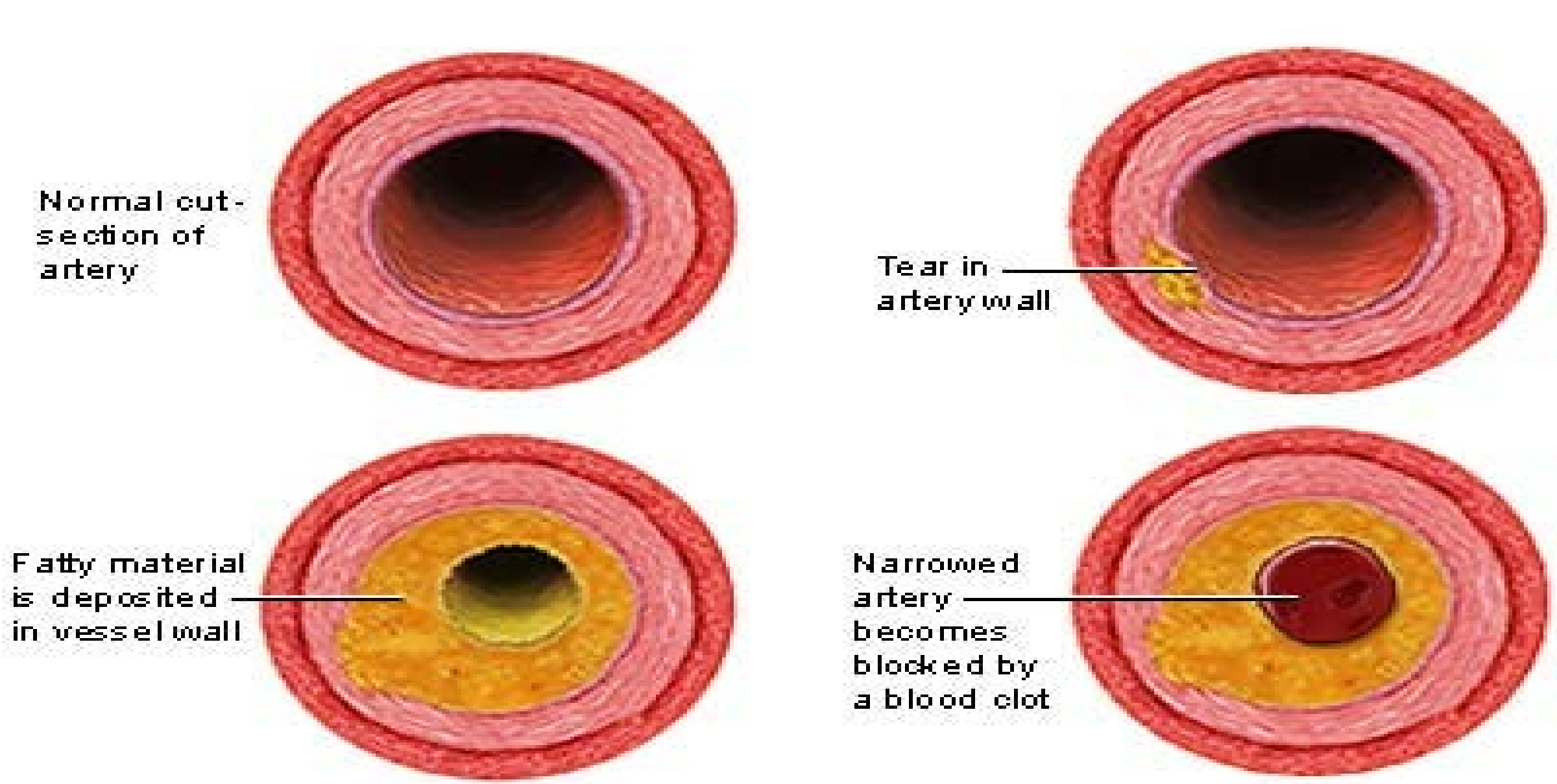
- Hypertension
- Diabetes
- Asthma
- Sleep Apnea
- Hyperlipidemia
- Arthritis
- Infertility
- Venous Stasis
- Depression

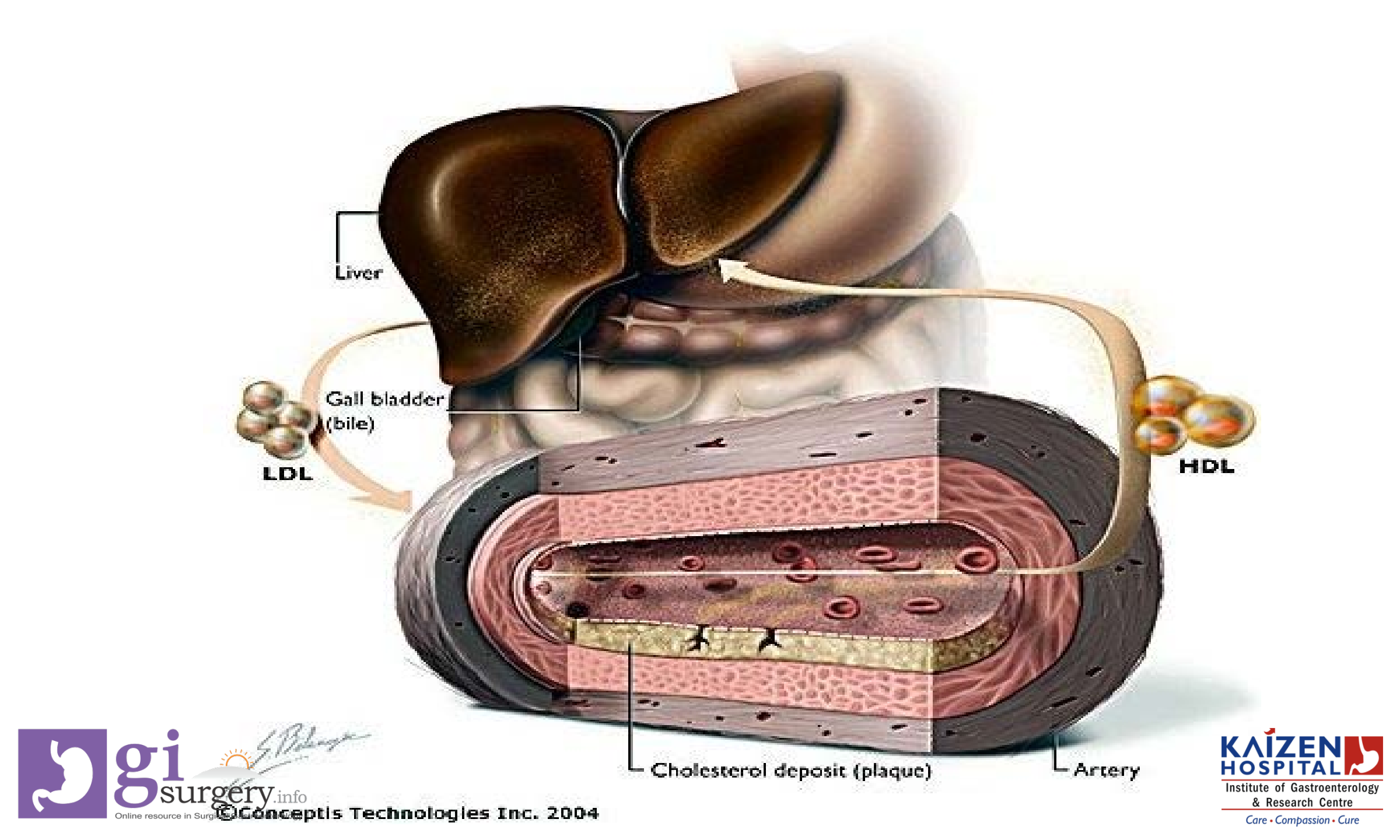
- Greater Cancer Risk
- Breast Cancer
- Colon Cancer
- Endometrial Cancer
- *All cancers except pancreatic cancer & prostate cancer

Benefits of 10% Weight Loss

Mortality	>20% fall in total mortality >30% fall in diabetes related deaths >40% fall in obesity related deaths
Blood pressure	fall of 10mmHg systolic and diastolic pressure
Diabetes	50% fall in fasting glucose
Lipids	10% dec. total cholesterol 15% dec. in LDL 30% dec. in triglycerides 8% inc. in HDL

Jung 1997





Risk Factors

Cannot be changed	Can be changed	
	Pathophysiologic Factors	Life-style factors
Age	High blood pressure	Tobacco use
Gender	Diabetes	Obesity
Race/Ethnic background	High Cholesterol	Sedentary/ inactivity
Heredity	Women: early menopause	Personality type/ coping ability
		Women: birth control pills

Obesity- Medical Management

First Line Rx - ***BED***

<u>BEHAVIOR MODIFICATION</u>

- Eat 3 times per day
- No Snacking Between Meals (Water Only)
- No Eating after 7:00 pm

<u>EXERCISE</u>

- Walk one half hour per day (Continuous)

<u>DIET CHANGES</u>

- Low calory
- High Fibres
- Frequency
- Breakfast

Take measurements of:

- height and weight: calculate BMI
- waist circumference
- neck circumference
- blood pressure and resting pulse rate

Check for:

- any evidence of cardiac valvular disease
- any evidence of pulmonary hypertension, cor pulmonale or congestive cardiac failure
- signs of dyslipidaemia
- signs of thyroid disease
- ophthalmic evidence for sustained hypertension or diabetic retinopathy in a diabetic patient
- any evidence of diabetes mellitus

Criteria for selecting obese patients suitable for anti-obesity drug therapy

- Drug treatment may be appropriate where diet and exercise have not achieved acceptable weight loss relative to associated medical risk.
- In such patients, drug treatment may be appropriate for
  - those whose BMI is ≥30
  - those with established comorbidities whose BMI is ≥27, if the drug licence permits.
- Weight lowering drugs should be targeted at those at high risk from obesity, not at obesity alone.

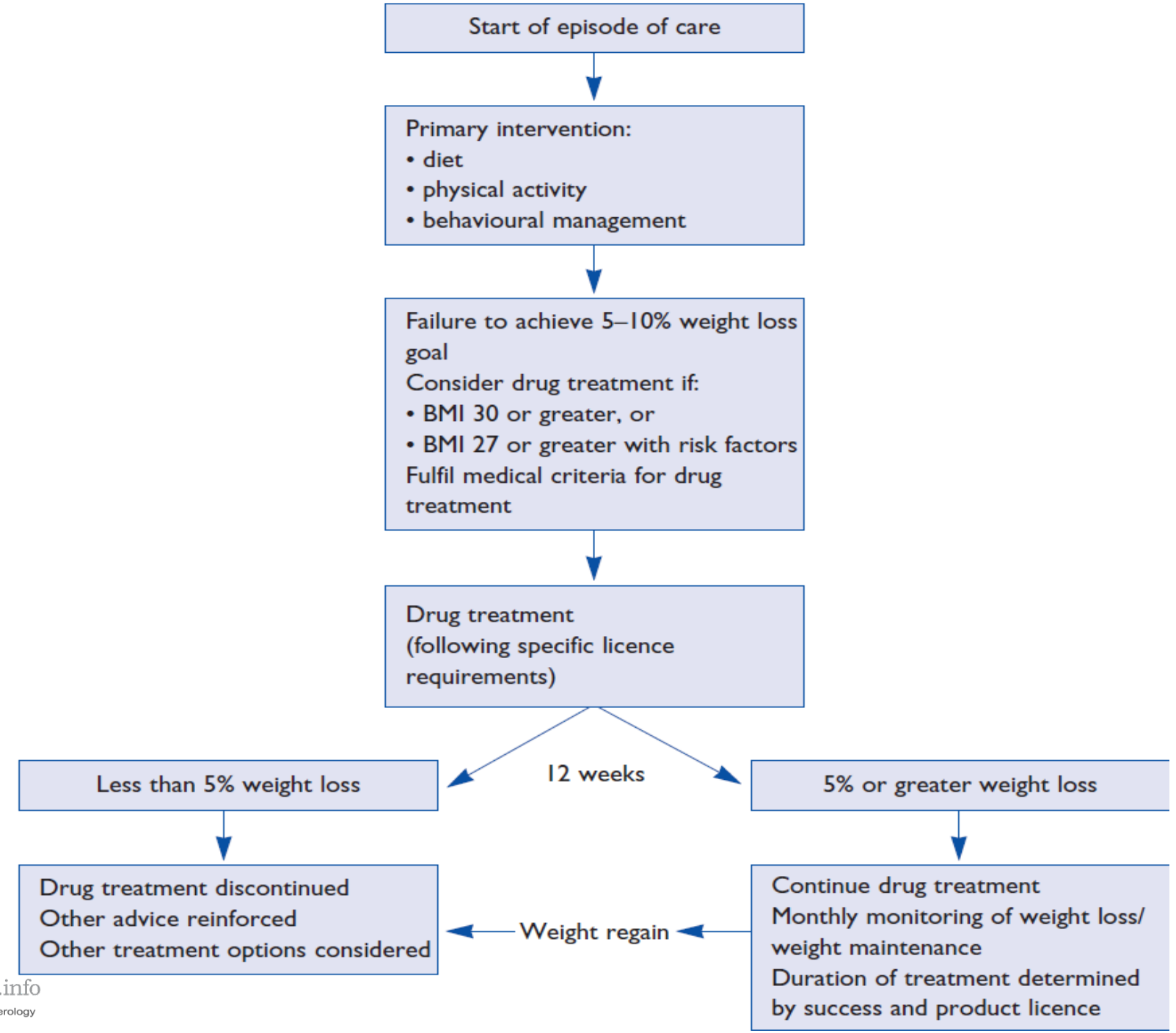
RCP Guidelines

The following groups should have priority for drug treatment:

- Patients with established comorbidities such as type 2 diabetes, hypertension, dyslipidaemia

- Patients who are physically restricted by their weight either because of breathlessness or arthritis

- Patients considered to be at high risk – for example, those with family histories of overweight or obese parents who died prematurely from CHD or developed type 2 diabetes with complications.



DRUG THERAPY

Serotonergic agents (i) Fenfluramine (ii) Dexfenfluramine	▪ Currently withdrawn because of valvular heart disease
Mixed Nor-adrenergic-serotonergic agent (i) Sibutramine	▪ 5-8% reduction weight over 6 months ▪ Weight loss maintain upto 1 year ▪ B.P., Pulse, drymouth, headache, insomnia & constipation
Reduce Nutrient Absorption (i) Orlistat	▪ Weight loss upto 9% ▪ Flatulence, fecal urgency, incontinence, steatorrhoea & frequency

Fenfluramine

- Introduced on the U.S. market in 1973
- Racemic mixture of two enantiomers, dextrofenfluramine and levofenfluramine
- Increases the level of the neurotransmitter serotonin
- Release of serotonin by disrupting vesicular storage of the neurotransmitter, and reversing serotonin transporter function
- The result is a feeling of fullness and loss of appetite.

- Withdrawn from the U.S. Market in 1997 after reports of heart valve disease and pulmonary hypertension, including cardiac fibrosis

- Thickening of the leaflet and chordae tendineae

- Damage to the heart valve continues long after stopping the medication

Phenteramine

- Psychostimulant drug of the phenethylamine class, with pharmacology similar to amphetamine

- Side effects consistent with its catecholamine-releasing properties, e.G., Tachycardia (increased heart rate) and elevated blood pressure
- Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, and headache
- Dryness of the mouth, unpleasant taste, diarrhea, constipation
- Psychological dependence

Orlistat

- Saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium Streptomyces toxytricini

Indications

- Those who have lost at least 2.5 kg in weight prior to consideration of drug treatment
- Patients requiring longer-term behavioural change Patients in whom a dietary assessment suggests high fat intake
- Patients with elevated LDL cholesterol values
- Patients with impaired glucose tolerance
- Patients who have repeatedly lost weight in the short-term and then rapidly regained it
- Those with an ability to adhere to a low fat diet for the longer term.

Contraindicated in

- Malabsorption
- Hypersensitivity to orlistat
- Reduced gallbladder function (e.g. after cholecystectomy)
- Pregnancy and breastfeeding
- Use caution with: obstructed bile duct, impaired liver function, and pancreatic disease

ADR:

- Steatorrhoea
- Urgency of defecation
- Fecal incontinence
- Fat absorbable vitamin deficiency
- 120 mg three times daily before meals

Phendimetrazine

- Stimulant drug of the morpholine chemical class
- Prodrug to phenmetrazine
- Acts as a norepinephrine-dopamine releasing agent
- 35 mg twice or thrice a day, 30 to 60 min before meals

Sibutramine

- Those whose appetites and eating habits are uncontrollable
- Frequent snackers
- Nocturnal eaters
- Those who need immediate weight loss for medical reasons
- Patients with low HDL cholesterol values
- Those with no contraindications to the use of sibutramine (specifically cardiac abnormalities or an elevated blood pressure, ie >140/90 mmHg on repeated measurements).

- Discontinued if the resting pulse rate is increased to more than 10 beats per minute and the blood pressure exceeds 145/95 mmHg.

- Lorcaserin
- Rimonabant
- Metformin
- Exenatide
- Pramlintide
- Topiramate

Measures	Immediate benefits	Longer-term benefits
Physical measures	Weight loss Reduction in waist circumference Improvement in comorbidities	Reduced breathlessness Decreased sleep apnoea Reduced angina Reduced blood pressure
Metabolic measures	Decreased fasting blood glucose and plasma insulin Improvement in fasting lipid profile Decreased HbA1c (if diabetic)	Reduction in doses of concomitant medications
Functional measures	Increased mobility Decreased symptoms Improved well being and mood Improved health-related quality of life	Reduced time away from work Increased involvement in social activities Decreased number of consultations with health professionals

Essential elements of an appropriate setting for anti-obesity drug treatment

1. *Trained staff*
2. *Printed programme*
3. *Suitable equipment*
4. *Specified weight loss goals*
5. *Documentation*
6. *A clearly defined follow-up procedure*
7. *checklist of possible adverse drug effects*

Conjugated linoleic acid	Reduces body fat	Possibly effective	Upset stomach, nausea, loose stools
Khat	Reduces appetite	Proven anorectic	long term use (high dosage) may cause liver damage, heart problem
ECA Stack	Increases metabolism	Effective in Humans	severe skin reactions, irritability, nervousness, dizziness, trembling, headache, insomnia, profuse perspiration,dehydration, itchy scalp and skin, vomiting, hyperthermia,irregular heartbeat, seizures, heart attack, stroke, or death

Obesity- Advantages of Surgery

- RESULTS:
- Hypertension 62-73% Cured
- Diabetes Mellitus 75-85% Cured
- Sleep Apnea 90% Cured
- GERD 90% Cured
- Dyslipidemia 34% Cured (38% improved)
- Hypertension & Dyslipidemia = @ 10 yrs.

Obesity- Advantages of Surgery

RESULTS:

- Dramatic Reduction in Weight
- Marked Quality of Life Improvement Depression, Self-esteem, eating pathology,

Poor results after Surgery

RESULTS: (Non-Compliance with Behavior & Exercise)

- Depression 12%
- Sexual Concerns 4%
- Relationship Problems 2% (>90%)
- Medical Complications due to Surgery 9%
- Lack of Exercise Being the Most Likely Area of Non-Compliance