Pathology of lipid metabolism. Metabolic syndrome concept. Biochemical aspects of nutritiology

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Pathology of lipid metabolism

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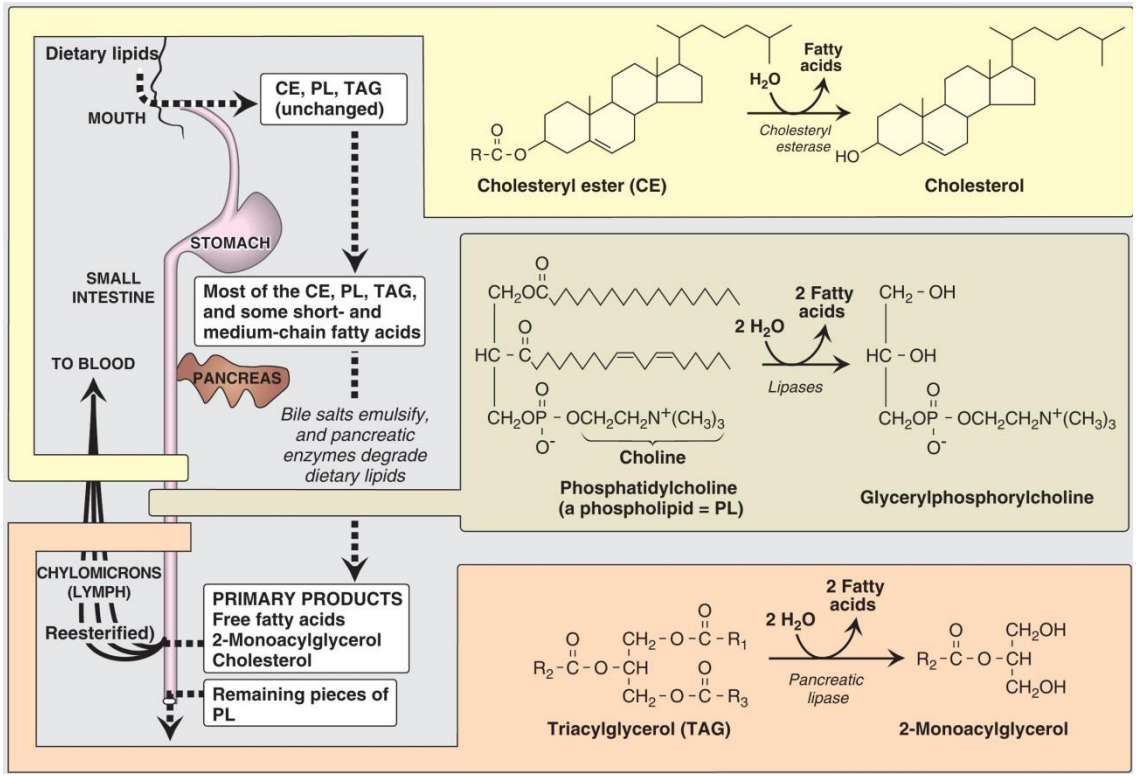
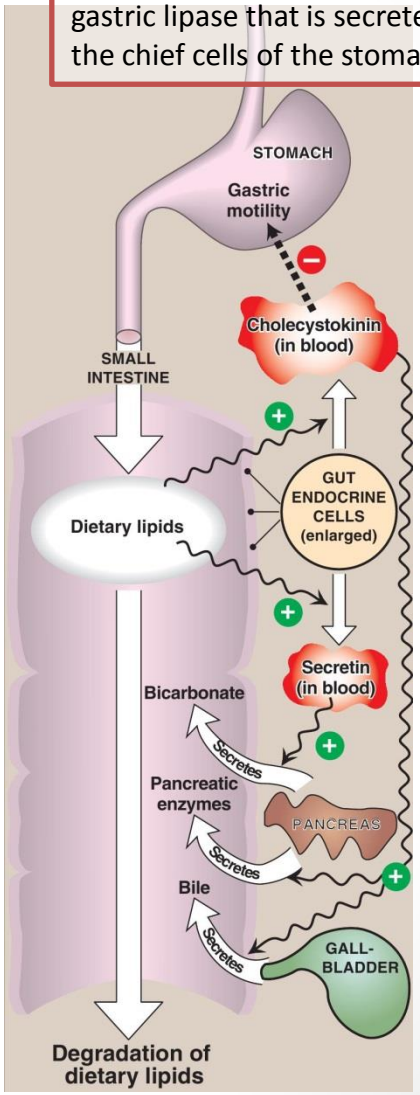
7. Lipidosis - hereditary violations of lipid metabolism.

Features of digestion and absorption and transport in the body

10% to 20% of dietary fat is digested by an acid-tolerant gastric lipase that is secreted by the chief cells of the stomach.





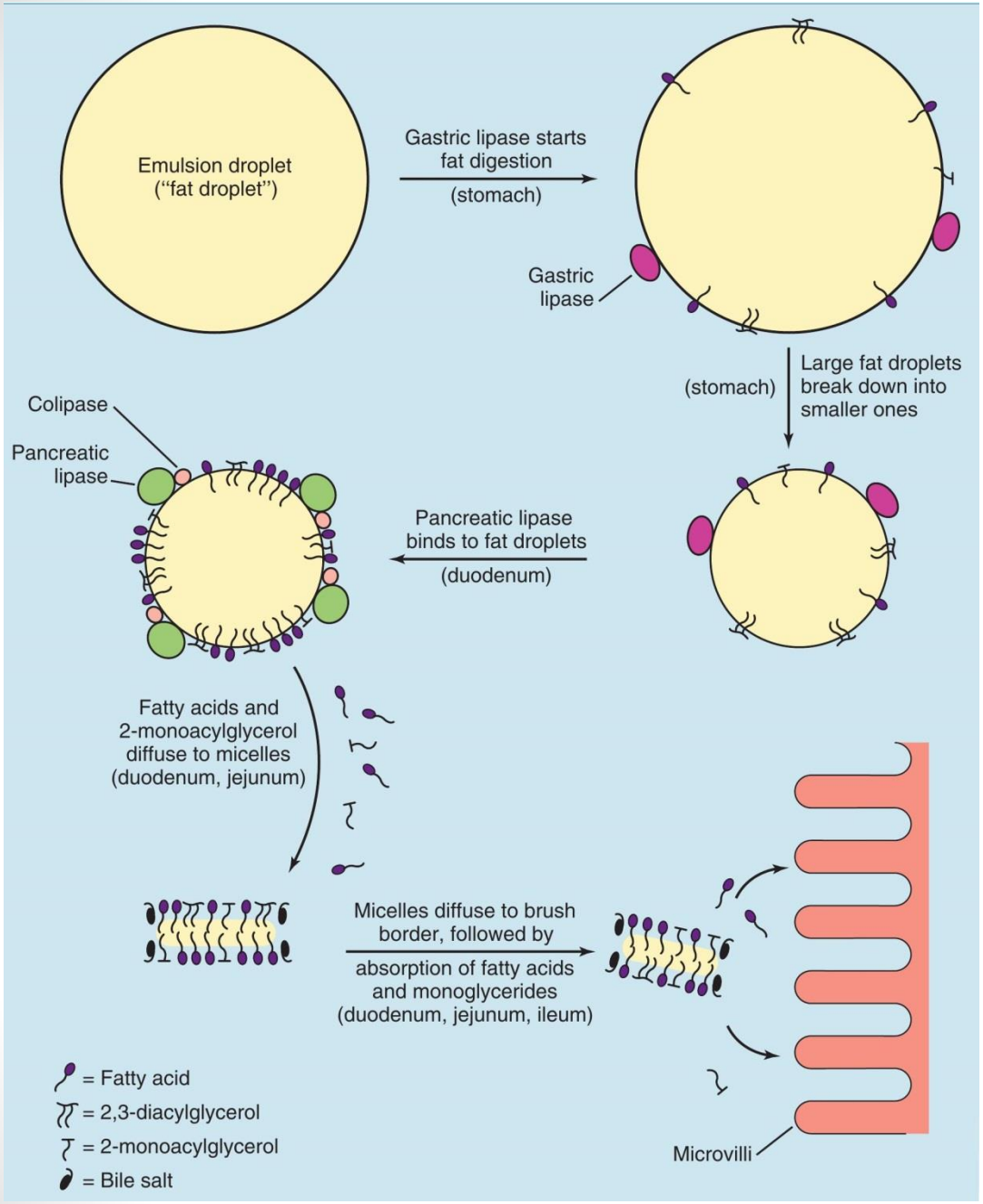
The digestion of dietary lipids begins in the stomach and continues in the small intestine.

Hydrophobic nature of lipids: dietary lipids (particularly with long-chain length fatty acids) be emulsified for efficient degradation.

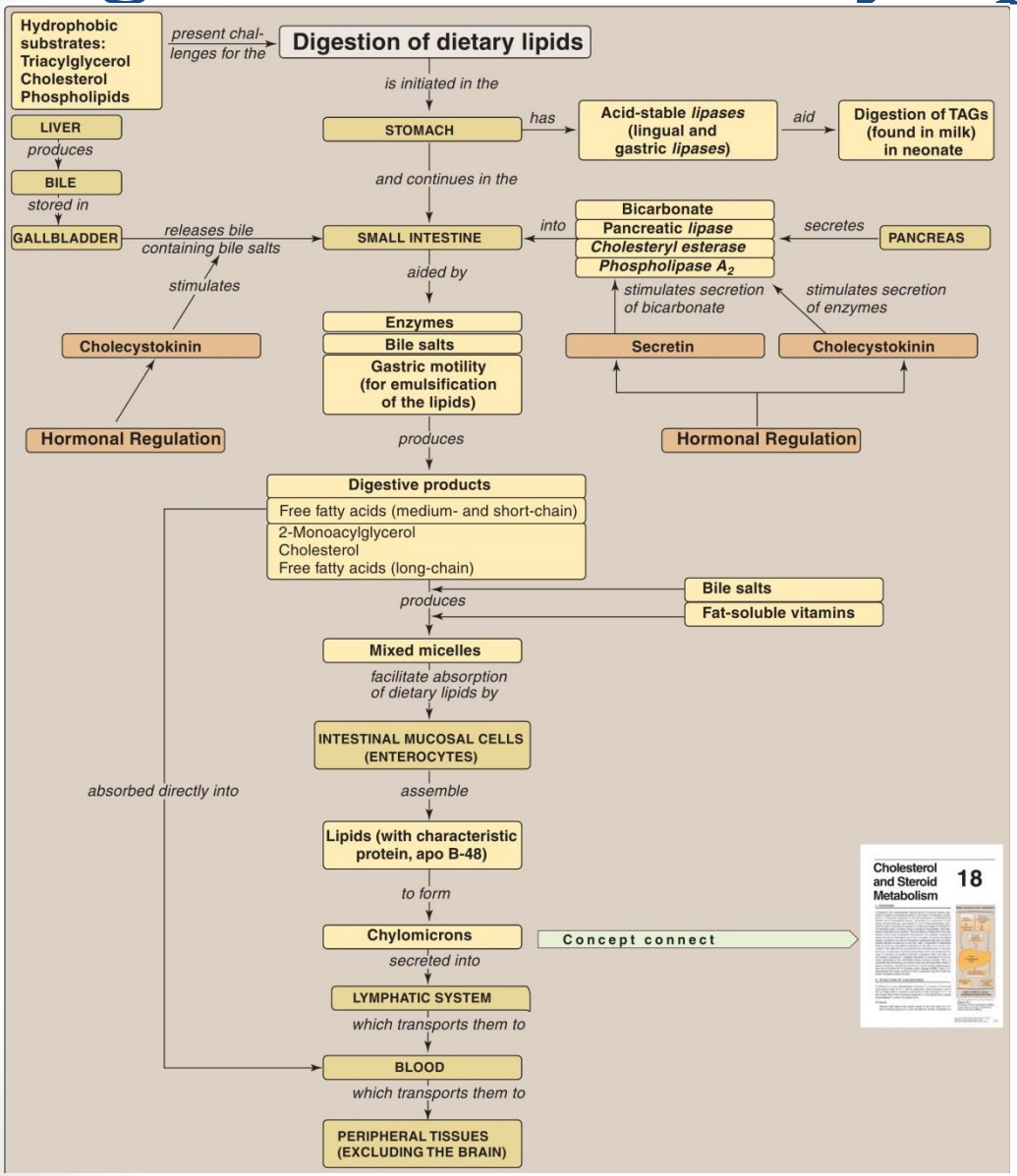
Fat digestion requires bile salts

- TAGs do not dissolve in water.
  - form large fat droplets => small surface area for enzymatic attack,
  - disperse the fat into smaller particles => ↑ surface/volume ratio.
- During ***mastication***, fat is emulsified with the help of
  - dietary phospholipids and proteins.
- In the ***stomach*** this process continues
  - fatty acids, monoglycerides, and diglycerides formed by *gastric lipase*.
- In the ***small intestine***,
  - **pancreatic lipase** and **colipase**
  - bind to the surface of the emulsion droplets.
- The ***colipase*** maintains the activity of the *lipase* surrounded by bile salts (can inhibit its activity).
- ***Pancreatic lipase*** hydrolyzes dietary triglycerides to free fatty acids and 2-monoacylglycerol (2-monoglyceride).

Sequence of events in fat digestion



Digestion of dietary lipids keymap



The dietary lipids are emulsified in the small intestine (bile salts as detergent).

Primary products from enzymatic degradation:

- 2-monoacylglycerol,
- unesterified cholesterol,
- free fatty acids.
- plus fat-soluble vitamins.

mixed micelles are formed ➔ absorption by enterocytes.

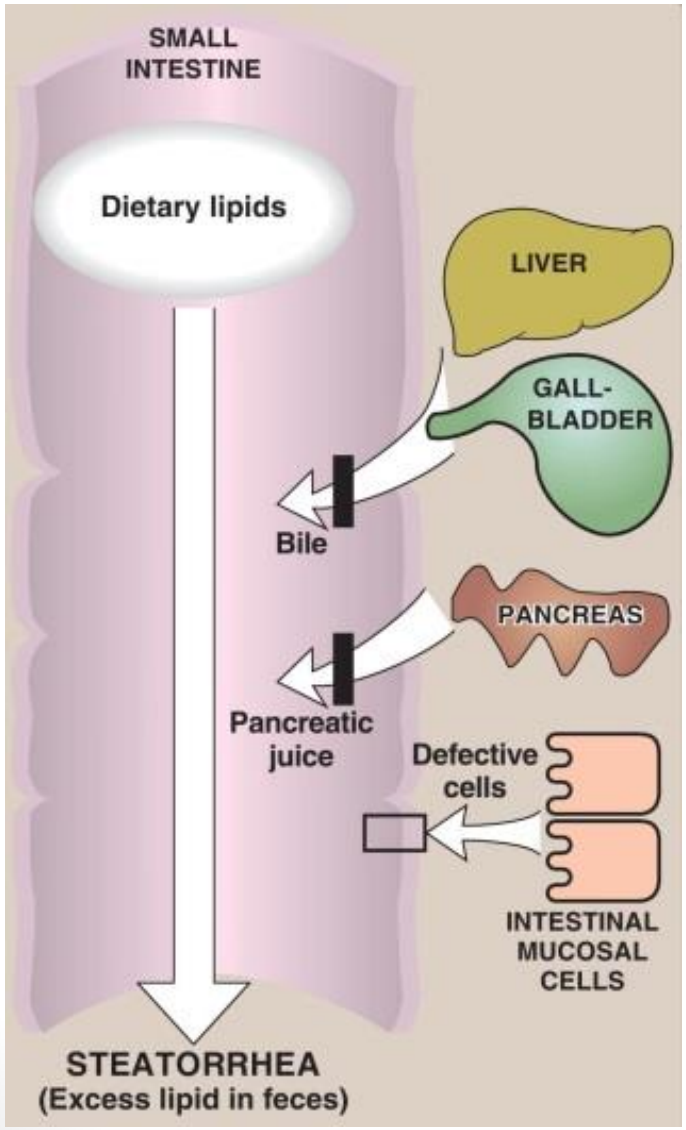
Resynthesize TAG, CE, and PL, synthesize apolipoprotein B-48 ➔ assembled into chylomicrons.

Released into the lymph ➔ to blood.

- Short- and medium chain fatty acids enter blood directly.

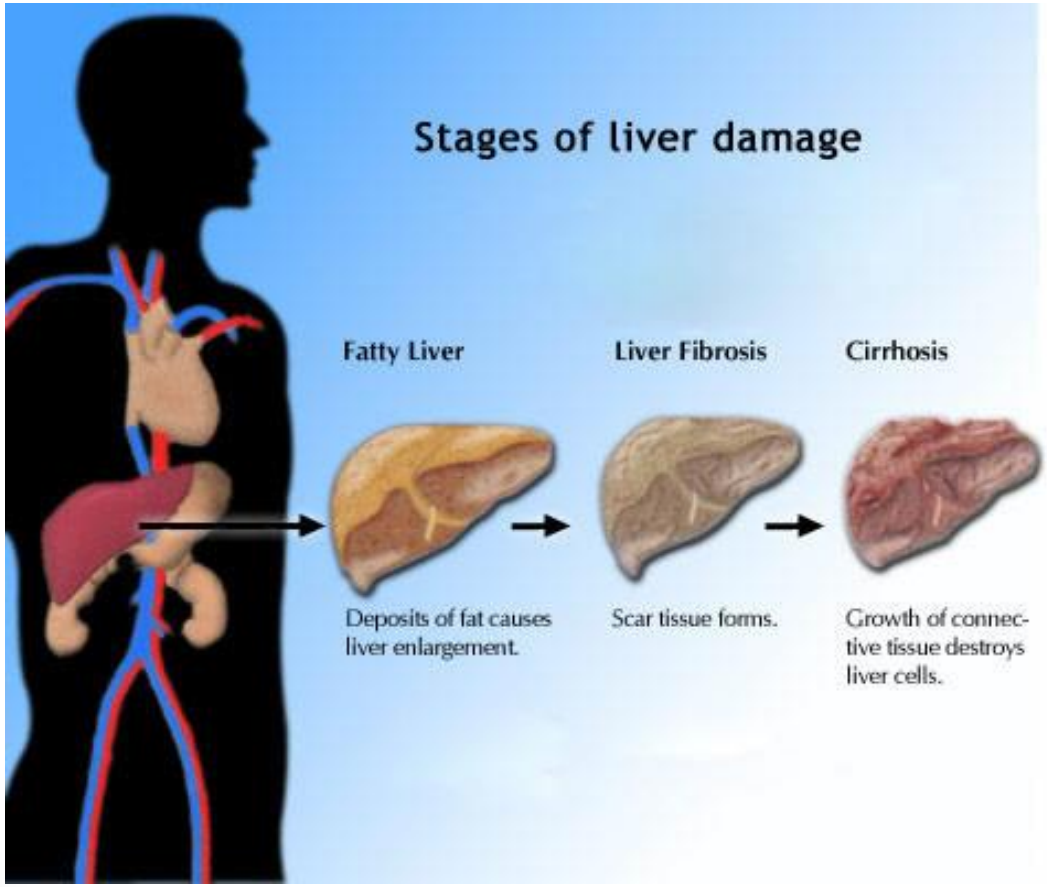
Thus, dietary lipids are transported to the peripheral tissues.

Impairments of lipids digestion and absorption, its manifestation. Steatorrhea



- **Lipid malabsorption** (disturbances in lipid digestion and/or absorption) ➔ increased lipid (incl. fat-soluble vitamins and essential FAs) in the feces (**steatorrhea**).
- Result from several conditions:
  - Cystic fibrosis (causing poor digestion);
  - Shortened bowel (causing decreased absorption).

Liver fat infiltration and degeneration: mechanisms of development and prevention

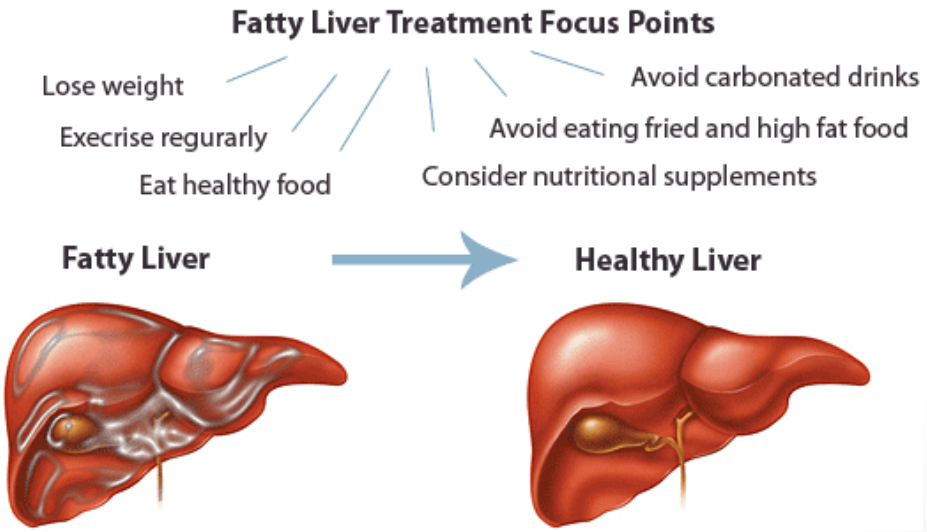


Liver Damaging Factors

- In a subset of individuals hepatic steatosis promotes an inflammatory response in the liver, referred to as steatohepatitis, which can progress to cirrhosis and liver cancer.

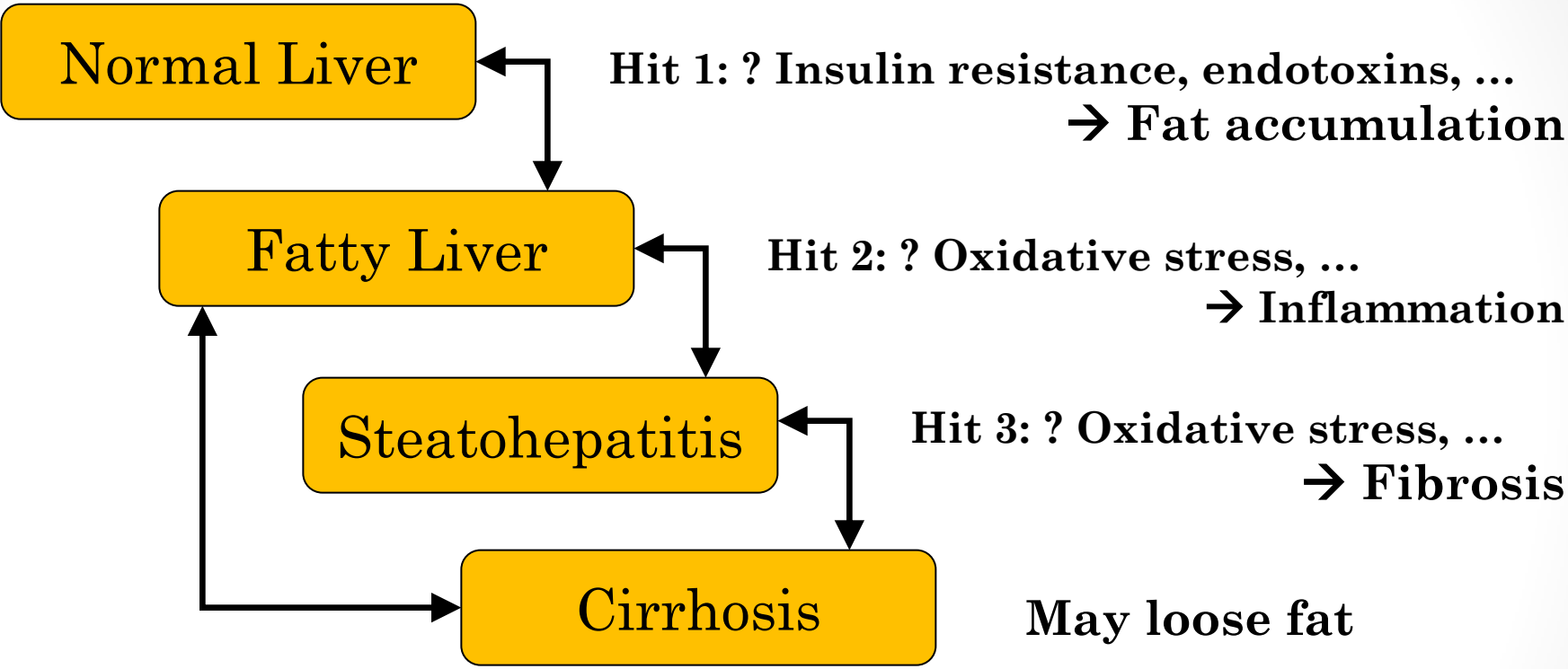
Fatty liver

- Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver disease in Western countries.
- The accumulation of excess triglyceride in the liver, a condition known as **hepatic steatosis** (or **fatty liver**), is associated with adverse metabolic consequences including insulin resistance and dyslipidemia.
- Factors promoting deposition of fat in the liver:
  - obesity,
  - diabetes,
  - insulin resistance,
  - alcohol ingestion.

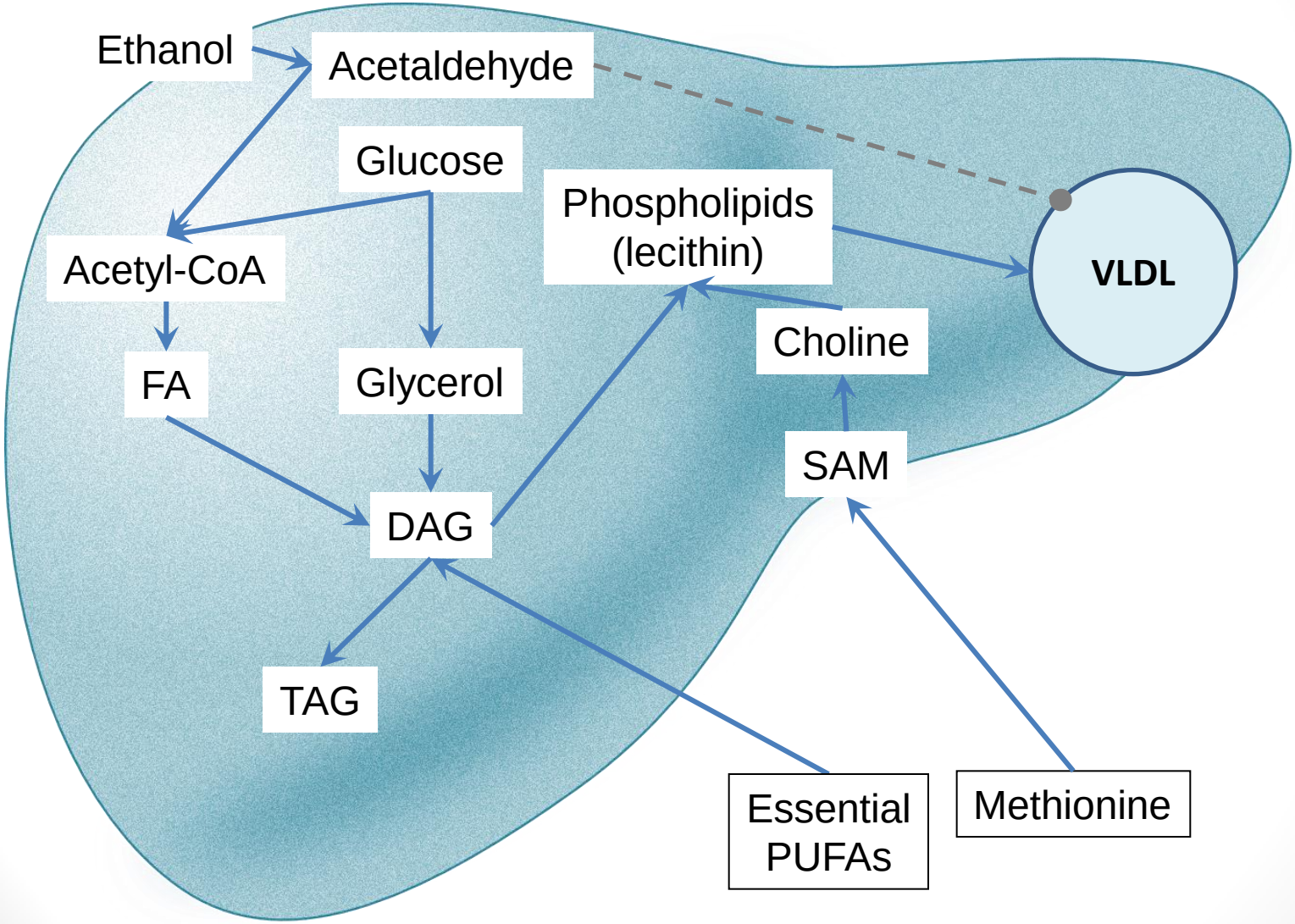


http://www.fatty-liver.com/treatment/

Multiple Hit Theory



Hepatoprotectors



Adipose tissue (white and brown). Their biological role

- Two types of adipose tissue with different locations, structures, colors, and pathologic characteristics.
- **White adipose tissue** (**WAT**, more common type) is composed of cells that, when completely developed, contain one large central droplet of whitish-yellow fat in their cytoplasm.
- **Brown adipose tissue (BAT)** contains cells with multiple lipid droplets interspersed among abundant mitochondria, which give these cells the darker appearance. Both types of adipose tissue have a rich blood supply.

WAT and BAT molecular characteristics

WAT: $UCP1^-$, $leptin^+$

BAT: $UCP1^+$, $leptin^-$

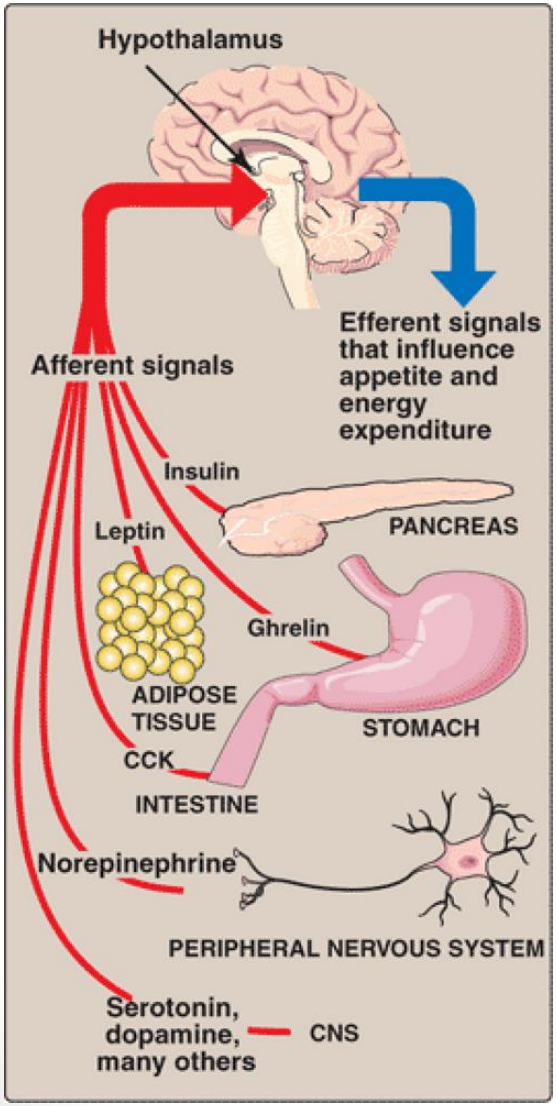
- WAT expression of leptin, but no expression of uncoupling protein 1 (UCP1)
- BAT expression of UCP, but no leptin.
- **Wisceral WAT** associated with abdominal and thoracic organs (but heart) secrets several inflammatory cytokines ➔ involved in **local and systemic inflammatory processes**.
- **Skeletal muscle associated WAT** secretes FFA, IL-6 and TNF-α ➔ formation of **insulin resistance**.
- **Cardiac tissue associated WAT** secretes cytokines – local inflammatory events and chemotaxis ➔ development of **atherosclerosis and systolic hypertension**.
- **Kidney associated WAT** involved in sodium reabsorption ➔ affects **intravascular volume and hypertension**.

Obesity - types, mechanisms of development and complications

Obesity is a disorder of body weight regulatory systems characterized by an accumulation of excess body fat.

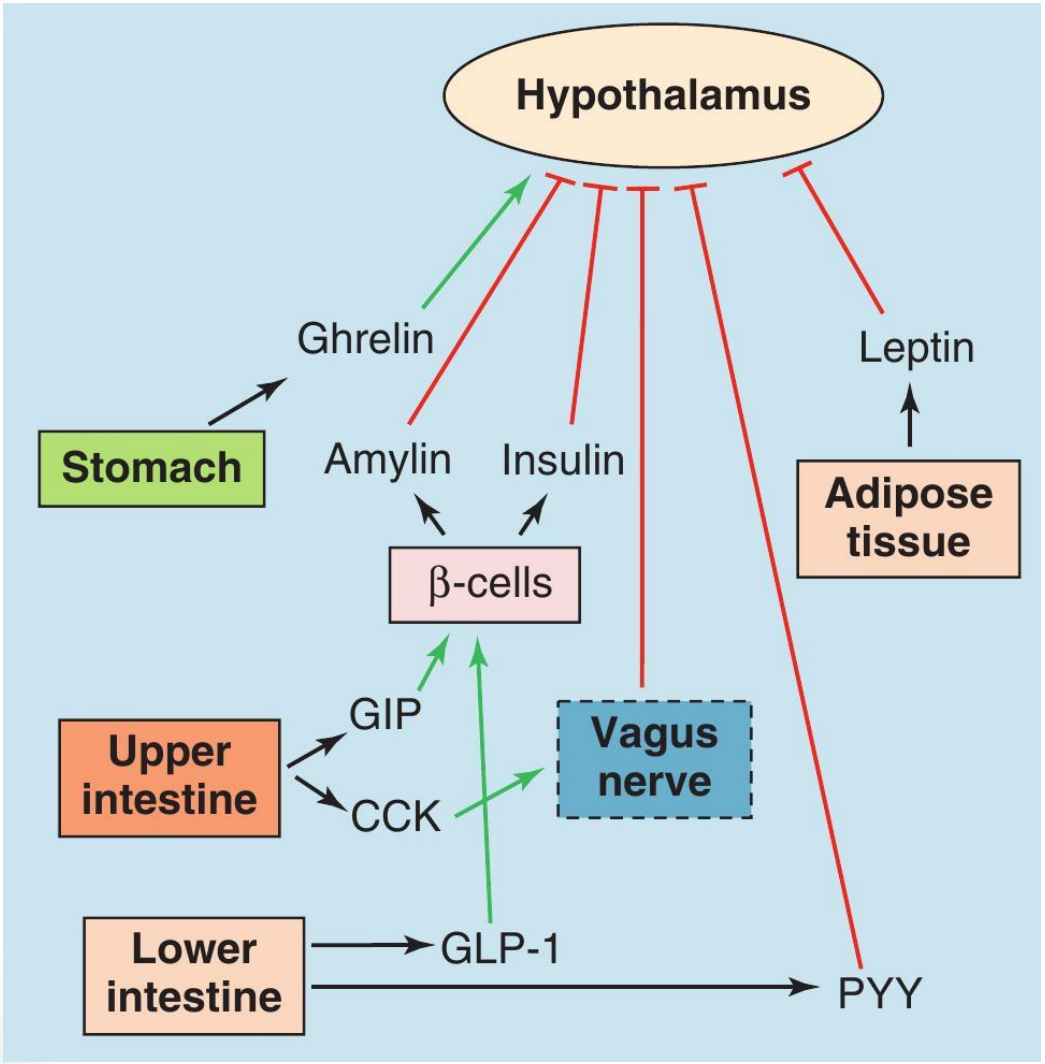
- The prevalence of obesity increases with age.
- risk of developing associated diseases: insuline resistance, type 2 diabetes, hypertension, gallbladder disease, and cardiovascular disease.
- Explosion of childhood obesity, 3-fold increase over the last two decades

Signaling in Obesity



- Obesity results when energy intake exceeds energy expenditure.
- Mechanism involves a complex interaction of biochemical, neurologic, environmental, and psychologic factors.
  - Afferent neural signals, circulating hormones, and metabolites affects the hypothalamus.
  - release of hypothalamic peptides,
  - activate efferent neural signals.

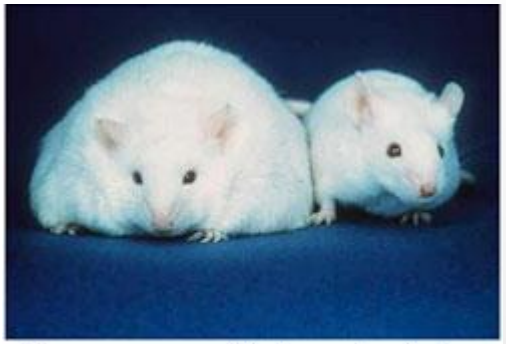
Some hormones in obesity control



- Important brain structures on which these hormones act include the ventromedial hypothalamus and the arcuate nucleus.
- **Ghrelin** is released when the **stomach is empty.**
- **Other** appetite-regulating **hormones** are released after a meal when **nutrients are abundant**.
  - CCK, Cholecystokinin;
  - GIP, gastric inhibitory polypeptide;
  - GLP-1, glucagon-like peptide-1;
  - PYY, peptide YY.

Body Weight Hormonal Regulation

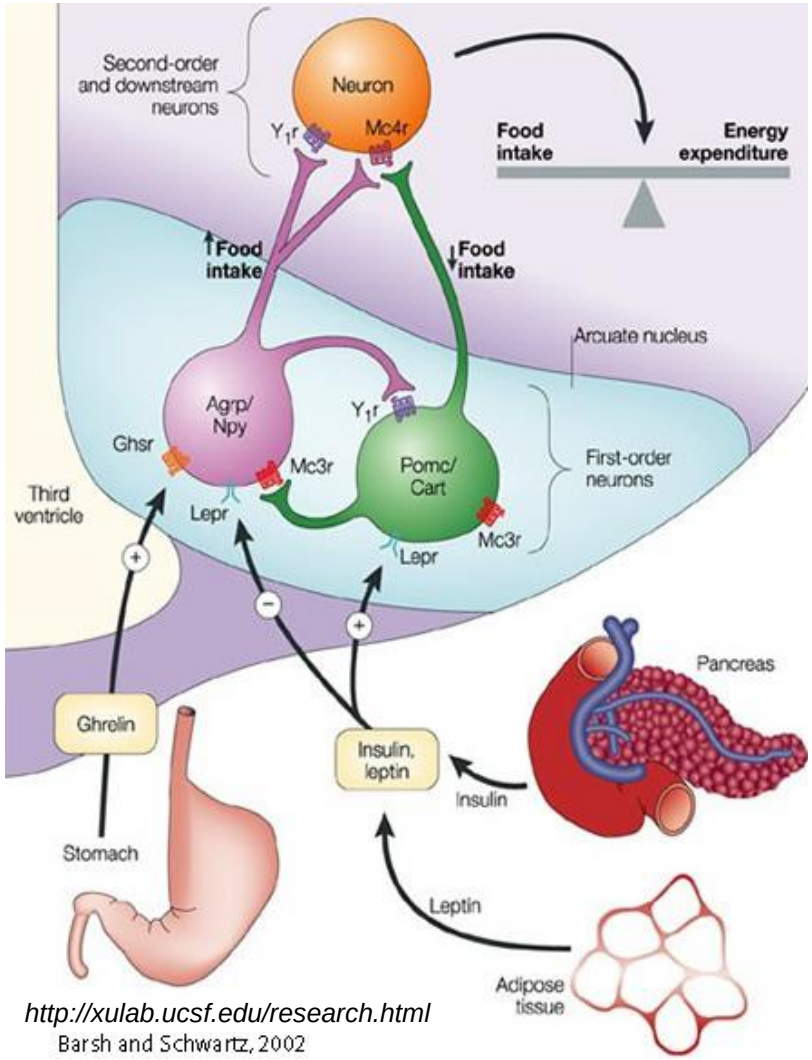
- Studies of the molecular genetics of mouse obesity have led to the isolation of at least six genes associated with obesity.
  - The most well-known mouse gene, named *ob* (for obesity), leads to severe hereditary obesity in mice.
- **Leptin,**
- **Ghrelin**, peptide secreted by the stomach; appetite-stimulating hormone.
  - Injection of ghrelin increases short-term food intake in rodents, and may decrease energy expenditure and fat catabolism.
- Peptides, such as **cholecystokinin**, released from the gut following ingestion of a meal can act as satiety signals to the brain.
- **Insulin** not only influences metabolism, but also promotes decreased energy intake.



knee-deepincortisol.blogspot.com

Obese mouse, unable to produce leptin, and normal mouse

The role of insulin, leptin, ghrelin, adiponectin and other hormones



http://xulab.ucsf.edu/research.html
Barsh and Schwartz, 2002

- 2 sets of neurons in the arcuate nucleus – **Agrp/Npy** and **Pomc/Cart**.
- Neuropeptides that stimulate food intake and decrease energy expenditure:
  - **Agrp** (agouti-related protein)
  - **Npy** (neuropeptide Y).
- Neuropeptides that inhibit food intake and increase energy expenditure:
  - **alpha-melanocyte stimulating hormone** (a derivative of proopiomelanocortin, Pomc)
  - **Cart** (cocaine- and amphetamine-regulated transcript).
- **Insulin** and **leptin** inhibit Agrp/Npy neurons and stimulate adjacent Pomc/Cart neurons.
- **Ghrelin** can activate Agrp/Npy neurons, stimulates food intake.
  - **Ghsr**, growth hormone secretagogue receptor;
  - **Lepr**, leptin receptor;
  - **Mc3r/Mc4r**, melanocortin 3/4 receptor;
  - **Y1r**, neuropeptide Y1 receptor.

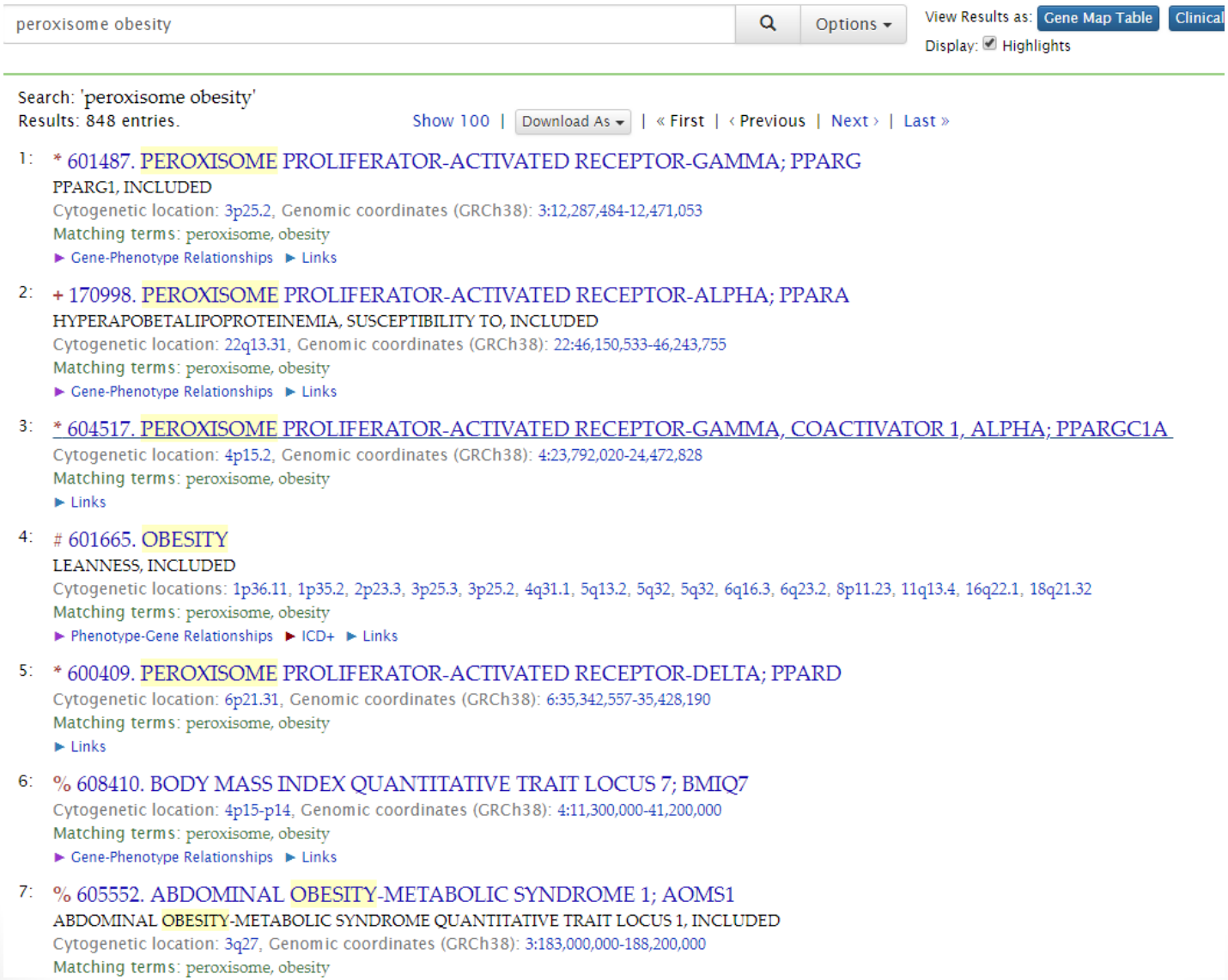
Obesity: phenotype-gene relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
1p36.11	Obesity, mild, early-onset	601665	AR, Mu, AD	3	NR0B2	604630
1p35.2	{Obesity, association with}	601665	AR, Mu, AD	3	SDC3	186357
2p23.3	{Obesity, early-onset, susceptibility to}	601665	AR, Mu, AD	3	POMC	176830
3p25.3	{Obesity, susceptibility to}	601665	AR, Mu, AD	3	GHRL	605353
3p25.2	Obesity, severe	601665	AR, Mu, AD	3	PPARG	601487
4q31.1	{Obesity, susceptibility to}	601665	AR, Mu, AD	3	UCP1	113730
5q13.2	{?Obesity, susceptibility to}	601665	AR, Mu, AD	3	CARTPT	602606
5q32	{Obesity, susceptibility to}	601665	AR, Mu, AD	3	ADRB2	109690
5q32	{Obesity, variation in}	601665	AR, Mu, AD	3	PPARGC1B	608886
6q16.3	Obesity, severe	601665	AR, Mu, AD	3	SIM1	603128
6q23.2	{Obesity, susceptibility to}	601665	AR, Mu, AD	3	ENPP1	173335
8p11.23	{Obesity, susceptibility to}	601665	AR, Mu, AD	3	ADRB3	109691
11q13.4	{Obesity, severe, and type II diabetes}	601665	AR, Mu, AD	3	UCP3	602044
16q22.1	{Obesity, late-onset}	601665	AR, Mu, AD	3	AGRP	602311
18q21.32	Obesity, autosomal dominant	601665	AR, Mu, AD	3	MC4R	155541

AR – autosomal-recessive; Mu – multifactorial; AD – autosomal-dominant.

http://omim.org/entry/601665

Search in OMIM "peroxisome obesity"



peroxisome obesity

Options

View Results as: Gene Map Table Clinical

Display: Highlights

Search: 'peroxisome obesity'
Results: 848 entries.

Show 100 | Download As | « First | ‹ Previous | Next › | Last »

1: * 601487. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA; PPARG
PPARG1, INCLUDED
Cytogenetic location: 3p25.2, Genomic coordinates (GRCh38): 3:12,287,484-12,471,053
Matching terms: peroxisome, obesity
► Gene-Phenotype Relationships ► Links

2: + 170998. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA; PPARA
HYPERAPOBETALIPOPROTEINEMIA, SUSCEPTIBILITY TO, INCLUDED
Cytogenetic location: 22q13.31, Genomic coordinates (GRCh38): 22:46,150,533-46,243,755
Matching terms: peroxisome, obesity
► Gene-Phenotype Relationships ► Links

3: * 604517. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA, COACTIVATOR 1, ALPHA; PPARGC1A
Cytogenetic location: 4p15.2, Genomic coordinates (GRCh38): 4:23,792,020-24,472,828
Matching terms: peroxisome, obesity
► Links

4: # 601665. OBESITY
LEANNESS, INCLUDED
Cytogenetic locations: 1p36.11, 1p35.2, 2p23.3, 3p25.3, 3p25.2, 4q31.1, 5q13.2, 5q32, 5q32, 6q16.3, 6q23.2, 8p11.23, 11q13.4, 16q22.1, 18q21.32
Matching terms: peroxisome, obesity
► Phenotype-Gene Relationships ► ICD+ ► Links

5: * 600409. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-DELTA; PPARD
Cytogenetic location: 6p21.31, Genomic coordinates (GRCh38): 6:35,342,557-35,428,190
Matching terms: peroxisome, obesity
► Links

6: % 608410. BODY MASS INDEX QUANTITATIVE TRAIT LOCUS 7; BMIQ7
Cytogenetic location: 4p15-p14, Genomic coordinates (GRCh38): 4:11,300,000-41,200,000
Matching terms: peroxisome, obesity
► Gene-Phenotype Relationships ► Links

7: % 605552. ABDOMINAL OBESITY-METABOLIC SYNDROME 1; AOMS1
ABDOMINAL OBESITY-METABOLIC SYNDROME QUANTITATIVE TRAIT LOCUS 1, INCLUDED
Cytogenetic location: 3q27, Genomic coordinates (GRCh38): 3:183,000,000-188,200,000
Matching terms: peroxisome, obesity

Insufficiency of peroxisome functions as a cause of obesity

OMIM * 601487

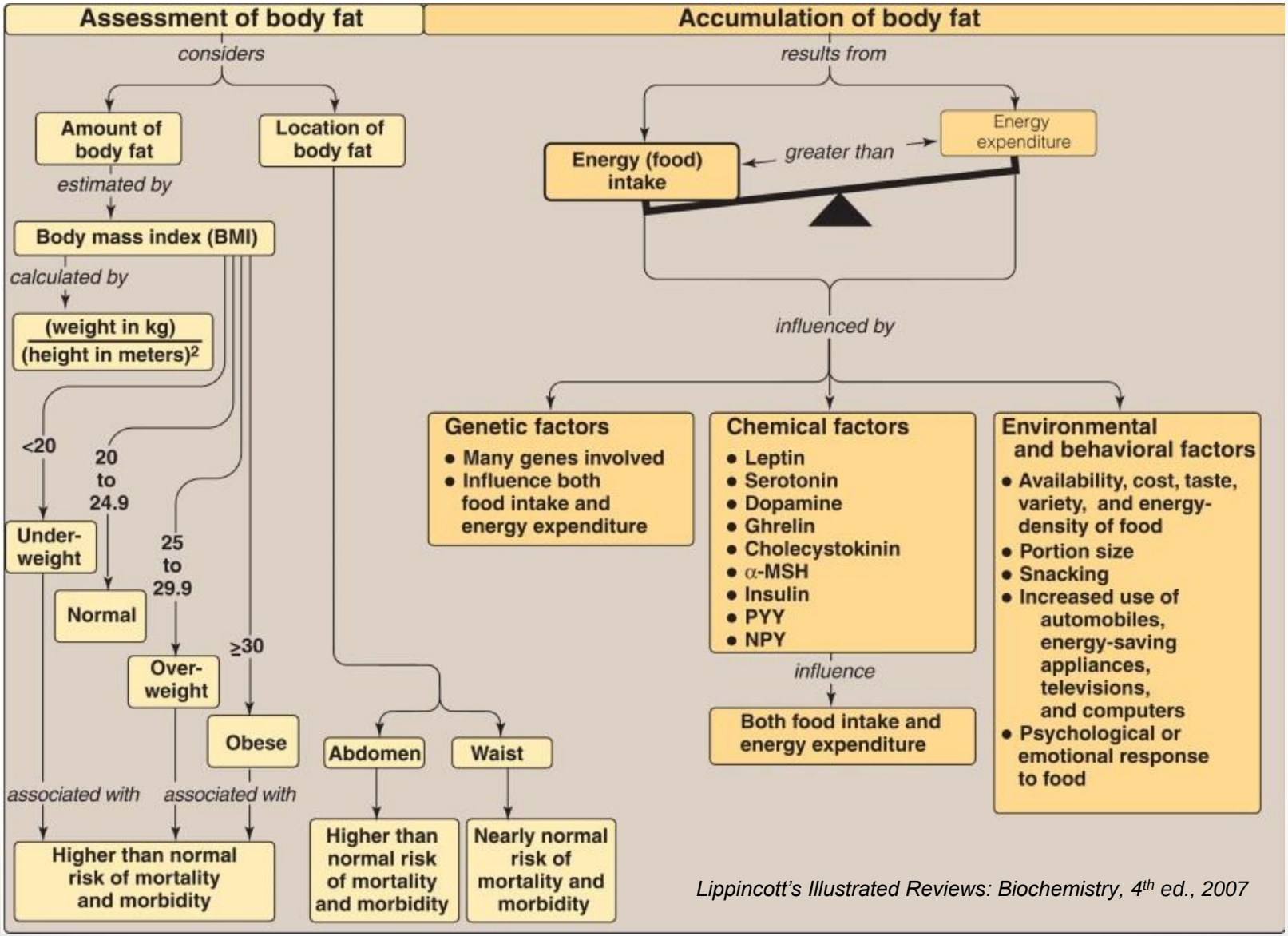
PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA; PPARG

Location	Phenotype	Phenotype MIM number	Inheritance
3p25.2	Carotid intimal medial thickness 1	609338	
	Insulin resistance, severe, digenic	604367	AD
	Lipodystrophy, familial partial, type 3	604367	AD
	Obesity, severe	601665	AR, Mu, AD
	[Obesity, resistance to]		
	{Diabetes, type 2}	125853	AD

Obesity Treatment

- Weight reduction: negative energy balance to reduce body weight: by decreasing caloric intake and/or increasing energy expenditure.
- All **diets** that lead to short-term weight loss.
  - Long-term maintenance of weight loss is difficult to achieve.
- Modest reduction in food intake occurs with **pharmacologic treatment**.
- **Surgical procedures** – for severely obese patient when other treatments were non effective.

Key Concept Map For Obesity



Lippincott's Illustrated Reviews: Biochemistry, 4th ed., 2007

Dislipoproteinemia. Classification by Friedrickson, biochemical and clinical-diagnostic characteristics of major groups

Hyperlipopro-einemia Type	*Increased plasma lipoprotein(s)*	*Increased plasma lipid (most)*	*Probable metabolic defect*	*Risk of atherosclerosis*	*Suggested treatment*
I	Chylomicrons	Triacylglycerols	Deficiency of lipoprotein lipase	May increase	Low fat diet
IIa	LDL	Cholesterol	Deficiency of LDL receptors	Very high (mostly in coronary artery)	Low cholesterol fat diet; cholestyramine
IIb	LDL and VLDL	Triacylglycerols and cholesterol	Overproduction of apo-B	— do —	— do —
III	IDL	Triacylglycerols and cholesterol	Abnormality in apo-E	Very high (mostly in peripheral vessels)	Low fat and low caloric diet; clofibrate
IV	VLDL	Triacylglycerols	Overproduction of TG	May or may not increase	Low fat and low caloric diet; niacin
V	Chylomicrons and VLDL	Triacylglycerols	—	— do —	— do —

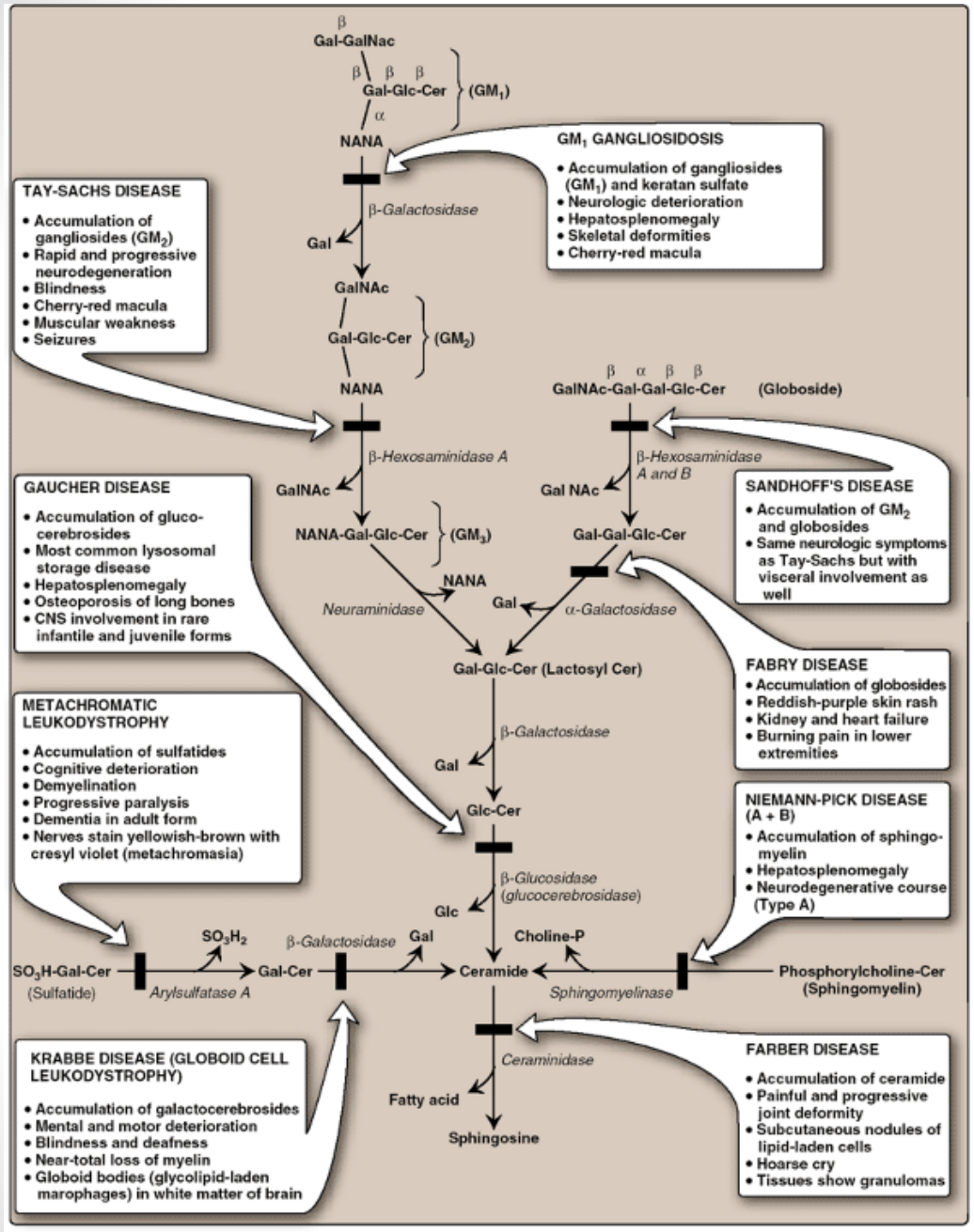
Frederickson's classification of hyperliporoteinemias - based on the electrophoretic patterns of plasma lipoproteins-is widely accepted to understand these disorder.

Lipidoses (Lipid Storage Diseases) – inborn errors of lipid metabolism Examples of sphigolipidoses

Disease	Enzyme Deficiency	Lipid Accumulating	Clinical Symptoms
Tay-Sachs disease	Hexosaminidase A	Cer—Glc—Gal(NeuAc)–÷–GalNAc G_{M2} Ganglioside	Mental retardation, blindness, muscular weakness
Fabry disease	α-Galactosidase	Cer—Glc—Gal—÷–Gal Globotriaosylceramide	Skin rash, kidney failure (full symptoms only in males; X-linked recessive)
Metachromatic leukodystrophy	Arylsulfatase A	Cer—Gal—÷–OSO_3 3-Sulfogalactosylceramide	Mental retardation and psychologic disturbances in adults; demyelination
Krabbe disease	β-Galactosidase	Cer—÷–Gal Galactosylceramide	Mental retardation; myelin almost absent
Gaucher disease	β-Glucosidase	Cer—÷–Glc Glucosylceramide	Enlarged liver and spleen, erosion of long bones, mental retardation in infants
Niemann-Pick disease	Sphingomyelinase	Cer—÷–P—choline Sphingomyelin	Enlarged liver and spleen, mental retardation; fatal in early life
Farber disease	Ceramidase	Acyl—÷–Sphingosine Ceramide	Hoarseness, dermatitis, skeletal deformation, mental retardation; fatal in early life

Abbreviations: Cer, ceramide; Gal, galactose; Glc, glucose; NeuAc, *N*-acetylneuraminic acid; ÷, site of deficient enzyme reaction.

Harper's Illustrated Biochemistry, 30th Ed. (2015)



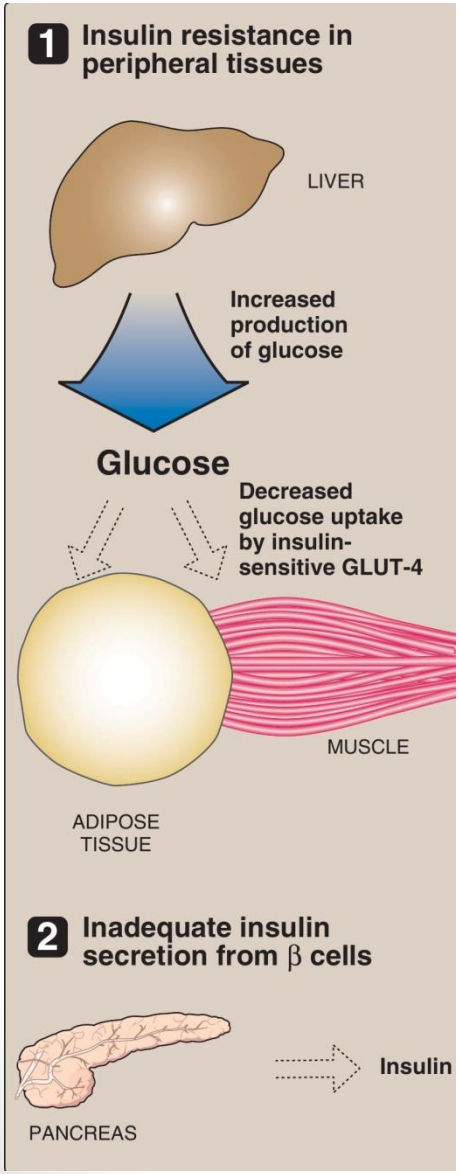
Lipidoses: Sphingolipidoses & Gangliosidoses

- Degradation of sphingolipids showing the enzymes affected in related genetic diseases, the sphingolipidoses.
- All of the diseases are autosomal recessive except Fabry disease, which is X-linked, and all can be fatal in early life.
- Cer = ceramide.

Metabolic syndrome concept

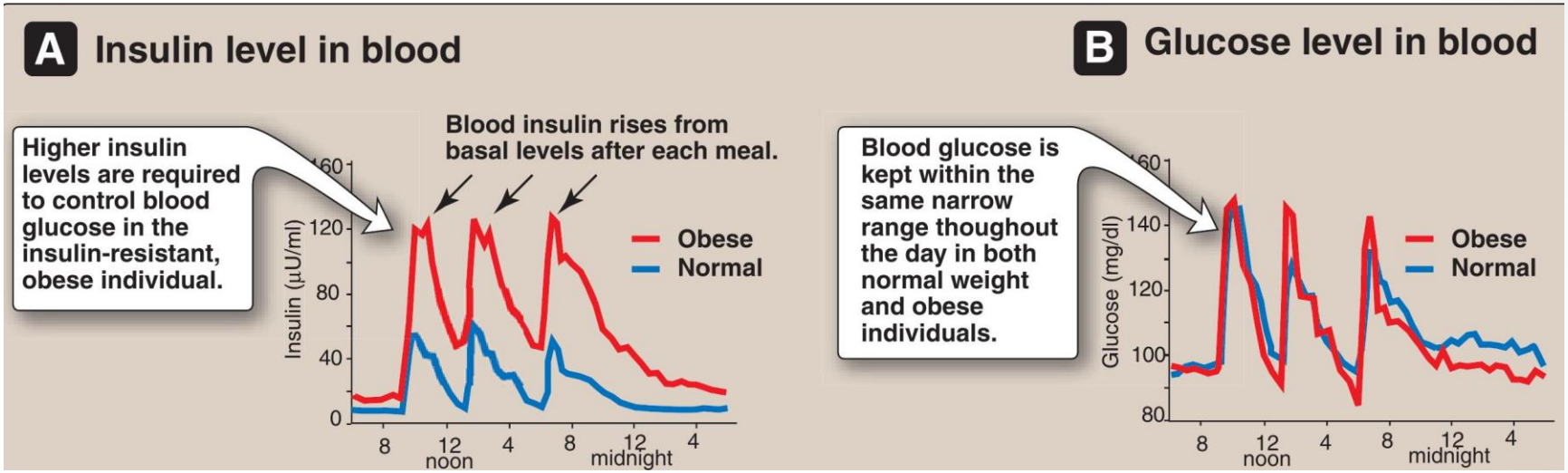
Metabolic syndrome. Molecular mechanisms of formation of resistance to insulin. Insulin resistance. Leptin resistance.

Insulin resistance formation



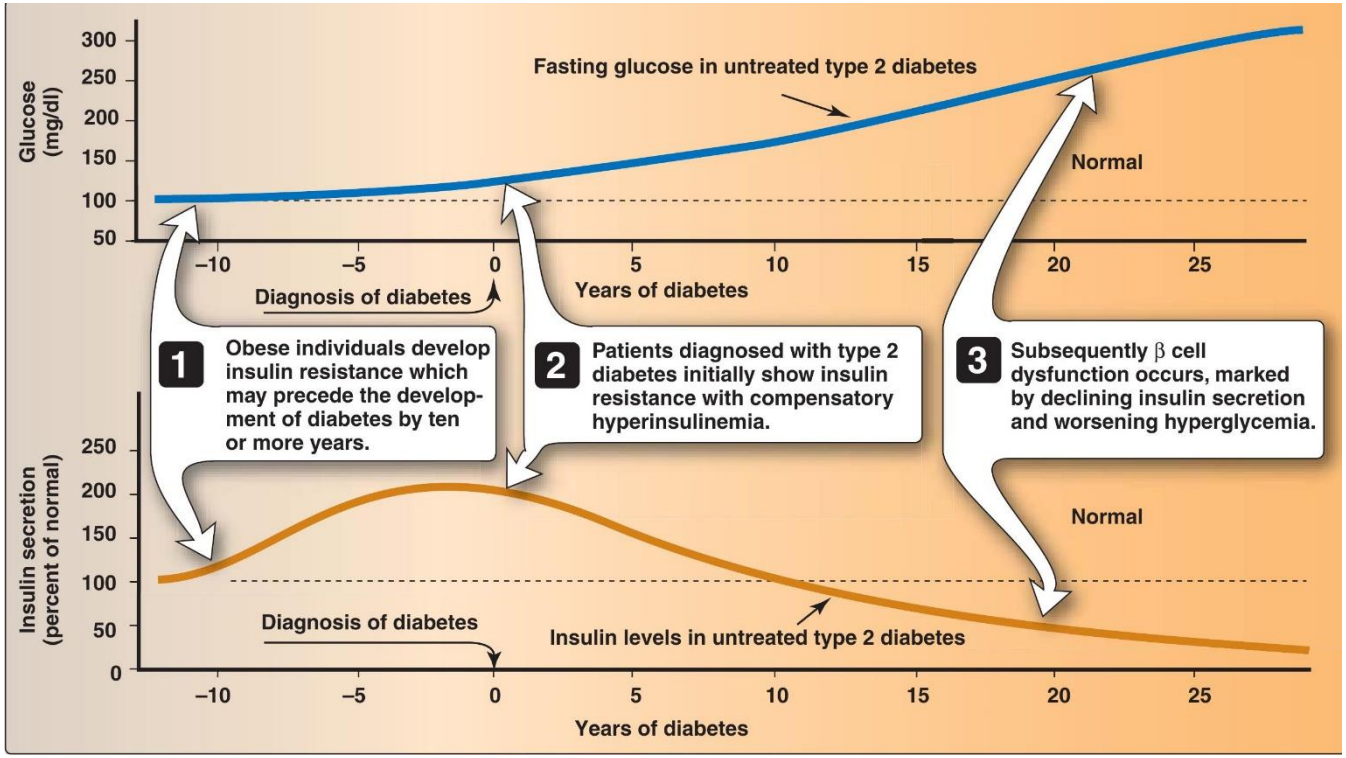
- Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion.
- **Insulin resistance** is the decreased ability of target tissues, (liver, adipose, and muscle) to respond properly to normal (or elevated) circulating concentrations of insulin.
  - Insulin resistance is characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue.
- **Insulin resistance and obesity:** Obesity is the most common cause of insulin resistance;
  - however, most people with obesity and insulin resistance do not become diabetic;
  - mainly due to compensation for insulin resistance with **elevated levels of insulin.**

Blood insulin and glucose levels in normal weight and obese subjects



- Insulin secretion is two to three times higher in obese subjects than it is in lean individuals.
  - This higher insulin concentration compensates for the diminished effect of the hormone (as a result of insulin resistance), and produces blood glucose levels similar to those observed in lean individuals.

Insulin resistance and type 2 diabetes



- Insulin resistance alone will not lead to type 2 diabetes.
  - Rather, type 2 diabetes develops in insulin-resistant individuals with impaired β-cell function.
  - Insulin resistance and risk for the development of type 2 diabetes is observed in the elderly, and in individuals who are obese, physically inactive, or in the 3-5% of pregnant women who develop ***gestational diabetes***.
  - These patients are unable to sufficiently compensate for insulin resistance with increased insulin release.

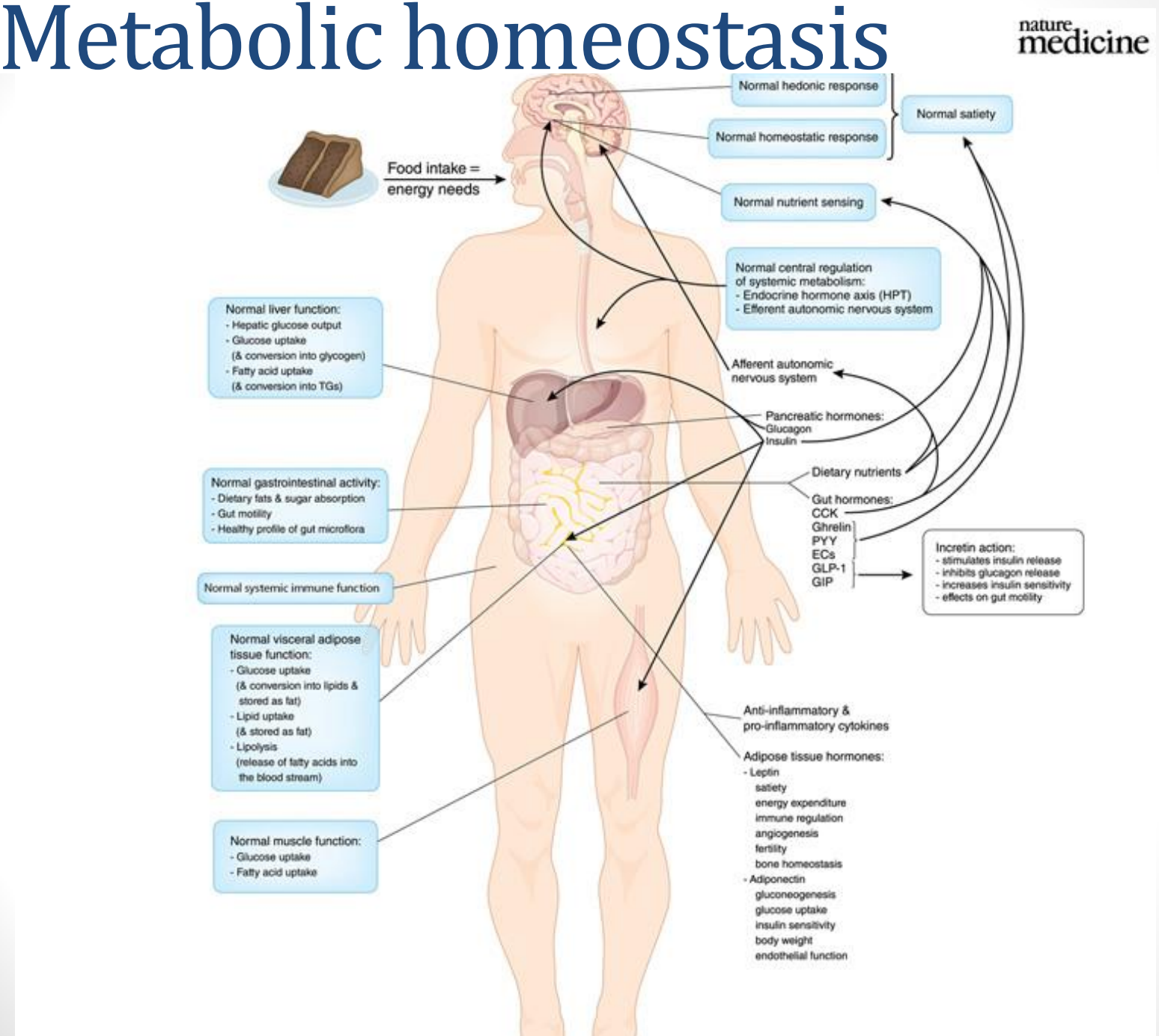
Insulin resistance increases with weight gain and diminishes with weight loss

- Fat accumulation is important in the development of insulin resistance.
- **Adipose tissue** is not simply an energy storage organ, but also a secretory organ.
- Regulatory substances produced by adipocytes include **leptin**, and **adiponectin**,
  - may contribute to the development of insulin resistance.
  - The elevated levels of free fatty acids (FFA) in obesity also implicated in the development of insulin resistance.
  - FFA also arise from lipolysis in insulin-resistant adipose.

Metabolic syndrome

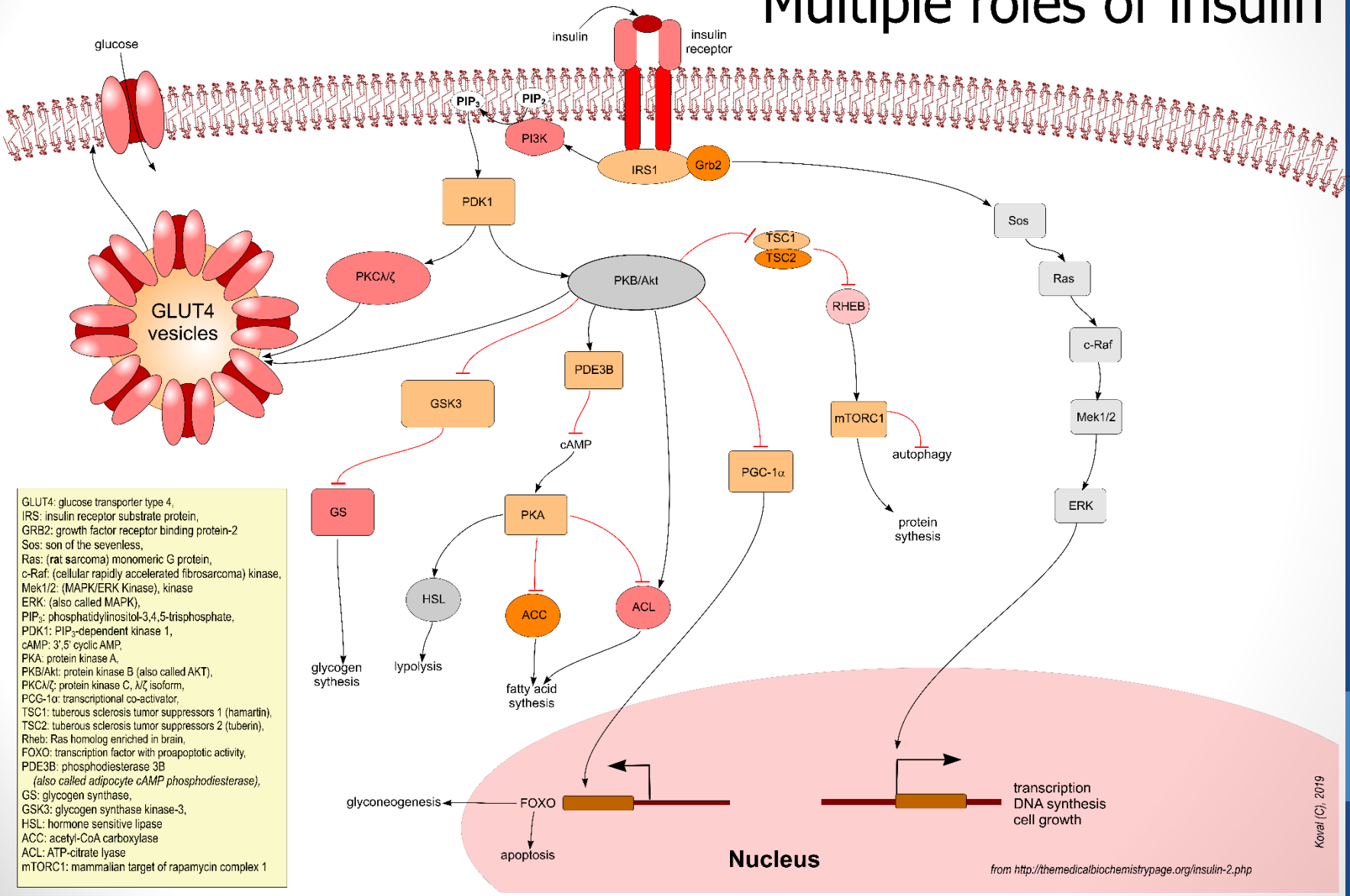
- Abdominal obesity is associated with a cluster of metabolic abnormalities that is referred to as the **metabolic syndrome** and includes
  - glucose intolerance,
  - insulin resistance,
  - hyperinsulinemia,
  - dyslipidemia (low high-density lipoprotein (HDL) and elevated triacylglycerols), and
  - hypertension.
- The metabolic syndrome is also associated with a state of chronic systemic inflammation that contributes to the pathogenesis of insulin resistance and atherosclerosis.
- In obesity, low levels of the adipocyte hormone adiponectin that normally dampens inflammation and sensitizes tissues, especially the liver, to insulin, may contribute to the metabolic syndrome and therefore the risk of type 2 diabetes and heart disease.

Metabolic homeostasis



Insulin receptor signaling

Multiple roles of insulin



GLUT4: glucose transporter type 4,
IRS: insulin receptor substrate protein,
GRB2: growth factor receptor binding protein-2
Sos: son of the sevenless,
Ras: (rat sarcoma) monomeric G protein,
c-Raf: (cellular rapidly accelerated fibrosarcoma) kinase,
Mek1/2: (MAPK/ERK Kinase), kinase
ERK: (also called MAPK),
PIP_3: phosphatidylinositol-3,4,5-trisphosphate,
PDK1: PIP_3-dependent kinase 1,
cAMP: 3',5' cyclic AMP,
PKA: protein kinase A,
PKB/Akt: protein kinase B (also called AKT),
PKCλ/ζ: protein kinase C, λ/ζ isoform,
PCG-1α: transcriptional co-activator,
TSC1: tuberous sclerosis tumor suppressors 1 (hamartin),
TSC2: tuberous sclerosis tumor suppressors 2 (tuberin),
Rheb: Ras homolog enriched in brain,
FOXO: transcription factor with proapoptotic activity,
PDE3B: phosphodiesterase 3B
(also called adipocyte cAMP phosphodiesterase),
GS: glycogen synthase,
GSK3: glycogen synthase kinase-3,
HSL: hormone sensitive lipase
ACC: acetyl-CoA carboxylase
ACL: ATP-citrate lyase
mTORC1: mammalian target of rapamycin complex 1

Mutations of insulin receptor

- Some inherited diseases due to mutations in insulin receptor:
  - Leprechaunism
  - Rabson-Mendenhall syndrome
  - Insulin-resistant diabetes mellitus with acanthosis nigricans
  - Familial hyperinsulinemic hypoglycemia

Leprechaunism

- **Leprechaunism (Donohue syndrome)** is a serious disorder caused by congenital absence of functional insulin receptors.
- This autosomal recessive disorder of insulin-resistance characterized by intrauterine and postnatal growth retardation, acanthosis nigricans, lipoatrophy, and genitomegaly.
  - The disease is known as ***leprechaunism*** because infants with the disease show an elf-like face and short stature.
  - Most die during the first years of life.

Leprechaun

Molecular Genetics of Donahue syndrome

- *Psiachou et al.* (1993) reported a female infant with leprechaunism who was homozygous by descent for a null allele of the insulin receptor gene.
  - The mutation involved replacement of a 13-bp sequence in exon 13 by an unrelated 5-bp sequence. The net deletion of 8 bp shifted the reading frame and introduced a premature chain termination downstream.
  - Both parents, who were first cousins, were heterozygous for the mutant allele and phenotypically and clinically normal.
- In affected members of a Yemeni family segregating Donahue syndrome, *Hone et al. (1994)* identified homozygosity for a substitution of met -> ile at codon 119 (exon 2) in the INSR gene.
  - The mutation was homozygous in all patients.
- Fernhoff (2004) noted that Donohue syndrome is a more appropriate designation for this disorder because 'leprechaunism' may be viewed as pejorative by families.

https://omim.org/entry/246200

Pejorative */pɪˈdʒɒrətɪv/, adjective:*
expressing contempt or disapproval. "permissiveness is used almost universally as a pejorative term"
synonims: disparaging, derogatory, denigratory, deprecatory, defamatory, slanderous, libellous, abusive, insulting, slighting, vituperative, disapproving, contemptuous.

Rabson-Mendenhall syndrome

- **Rabson-Mendenhall syndrome** is a rare disorder involving severe insulin resistance due to mutations in the insulin receptor gene.
- Obligatory symptoms are
  - extreme hyperinsulinemia and
  - profound insulin-resistance diabetes.
- Additional characteristics of RMS can include
  - acanthosis nigricans,
  - polycystic ovarian disease,
  - hirsutism,
  - precocity,
  - pineal hyperplasia, and
  - thick nails.

https://www.genome.jp/dbget-bin/www_bget?ds:H00942

Insulin-resistant diabetes mellitus with acanthosis nigricans

- Insulin-resistant diabetes mellitus with acanthosis nigricans (IRAN) is an unusual cause of diabetes that result from metabolic abnormalities associated with mutations of the INSR gene, characterized by phenotypic description of extreme insulin resistance, acanthosis nigricans, and hyperandrogenism.
- Other phenotype of IRAN form includes hirsutism and polycystic ovarian disease in a patient who is usually not obese.
- There is no distinctive serum marker.
  - Leprechaunism and the Rabson-Mendenhall syndrome also have mutations in INSR.

Familial hyperinsulinemic hypoglycemia

- Familial hyperinsulinemic hypoglycemia (HHF) is the most common cause of persistent hypoglycemia in infancy.
  - Specific genetic defects in the regulation of insulin secretion.
  - 7 loci have been associated with hyperinsulinism: *ABCC8*, *KCNJ11, HADHSC, GCK, GLUD1, SLC16A1*, and *INSR*.
    - Significant differences in phenotype and inheritance pattern.
  - The most common genes associated with hyperinsulinism, the *ABCC8* and *KCNJ11* genes that encode the 2 subunits of the β-cell **ATP-dependent potassium channel**.
  - Recessive mutations of these genes cause a **severe form of neonatal hypoglycemia** that frequently requires near-total pancreatectomy.
- **Diazoxide**, a drug an agonist of the ATP-dependent potassium channel to suppress insulin secretion,
  - effective when there are mutations of *GLUD1* and *HADHSC*.

Biochemical aspects of nutritiology.

- Energy needs of the human body (main consumption, thermogenic effect, physical activity, ambient temperature).
- Principles of rational nutrition. Macro- and micronutrients. Caloric value.
- Metabolism and energy in fasting, stress, and various types of physical activity and adaptation to it.
- Food behavior and hormones regulate it.
- Pathological conditions arising from eating disorders and nutritional imbalances (reduced immunity, allergies, diabetes, obesity, hypertension, cardiovascular disease, intestinal dysbacteriosis, chronic colitis, gastritis, infertility and decreased potency, growth and developmental disorders in children, etc.)

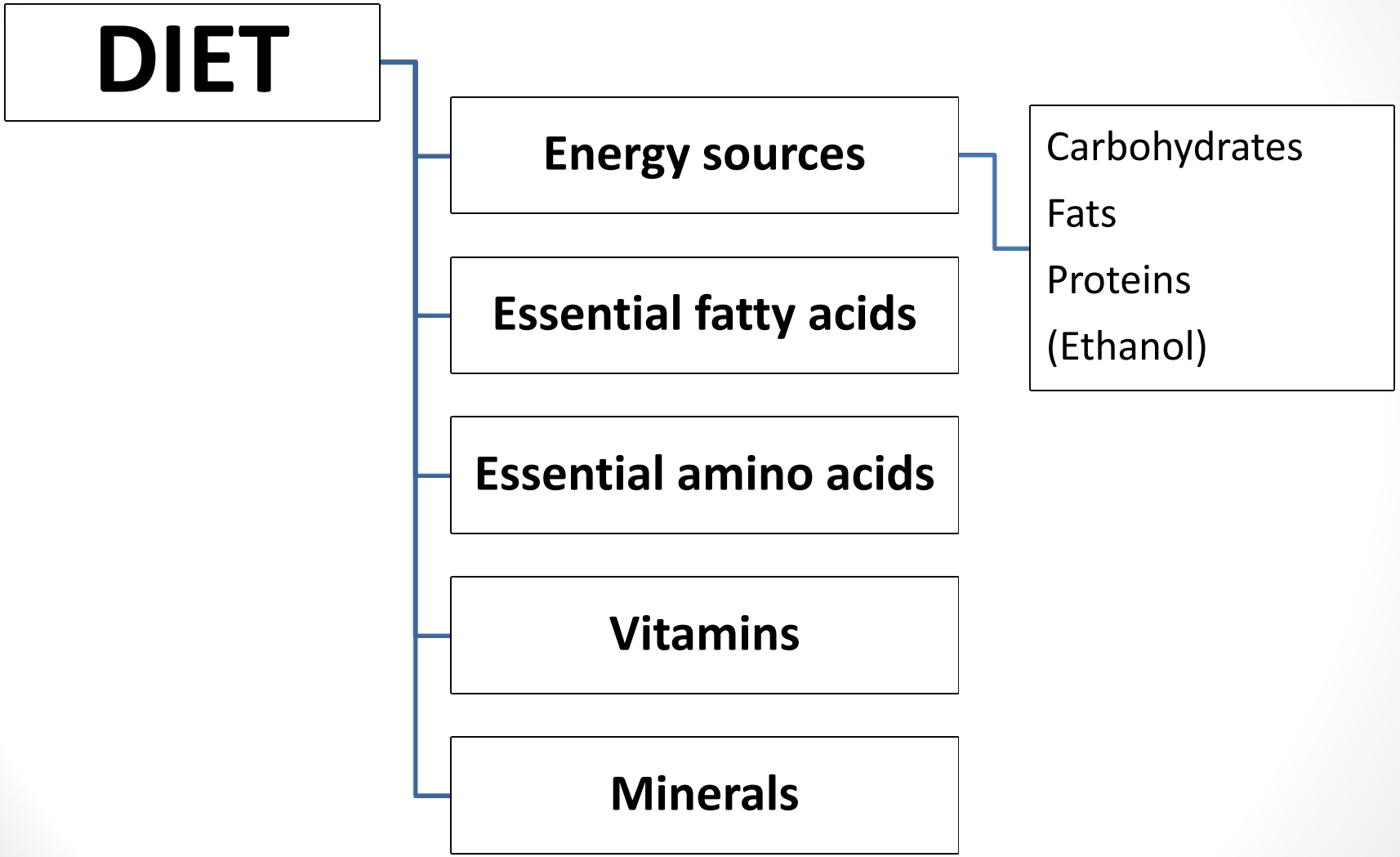
Definitions

- **nutrition**: the science of the nutrients in foods and their actions within the body. A broader definition includes the study of human behaviors related to food and eating.
- **foods**: products derived from plants or animals that can be taken into the body to yield energy and nutrients for the maintenance of life and the growth and repair of tissues.
- **chronic diseases**: diseases characterized by slow progression and long duration. Examples include heart disease, diabetes, and some cancers.
- • chronos = time
- **diet**: the foods and beverages a person eats and drinks.

6 classes of nutrients

Nutrient	Organic	Inorganic	Energy-yielding	Macronutrient	Micronutrient
Carbohydrates	✓		✓	✓	
Lipids (fats)	✓		✓	✓	
Proteins	✓		✓	✓	
Vitamins	✓				✓
Minerals		✓			✓
Water		✓			

Essential nutrients from the diet



MACRONUTRIENT	RANGE (percent of energy)
Fat	20–35
ω–6 Polyunsaturated fatty acids	5–10
ω–3 Polyunsaturated fatty acids	0.6–1.2*
(Approximately 10% of the total fat can come from longer-chain, ω–3 or ω–6 fatty acids.)	
Carbohydrate	45–65
● No less than 130 g/day	
(No more than 25% of total calories should come from added sugars.)	
Fiber	
● Men: 38 g	
● Women: 25 g	
Protein	10–35

Acceptable macronutrient distribution ranges in adults

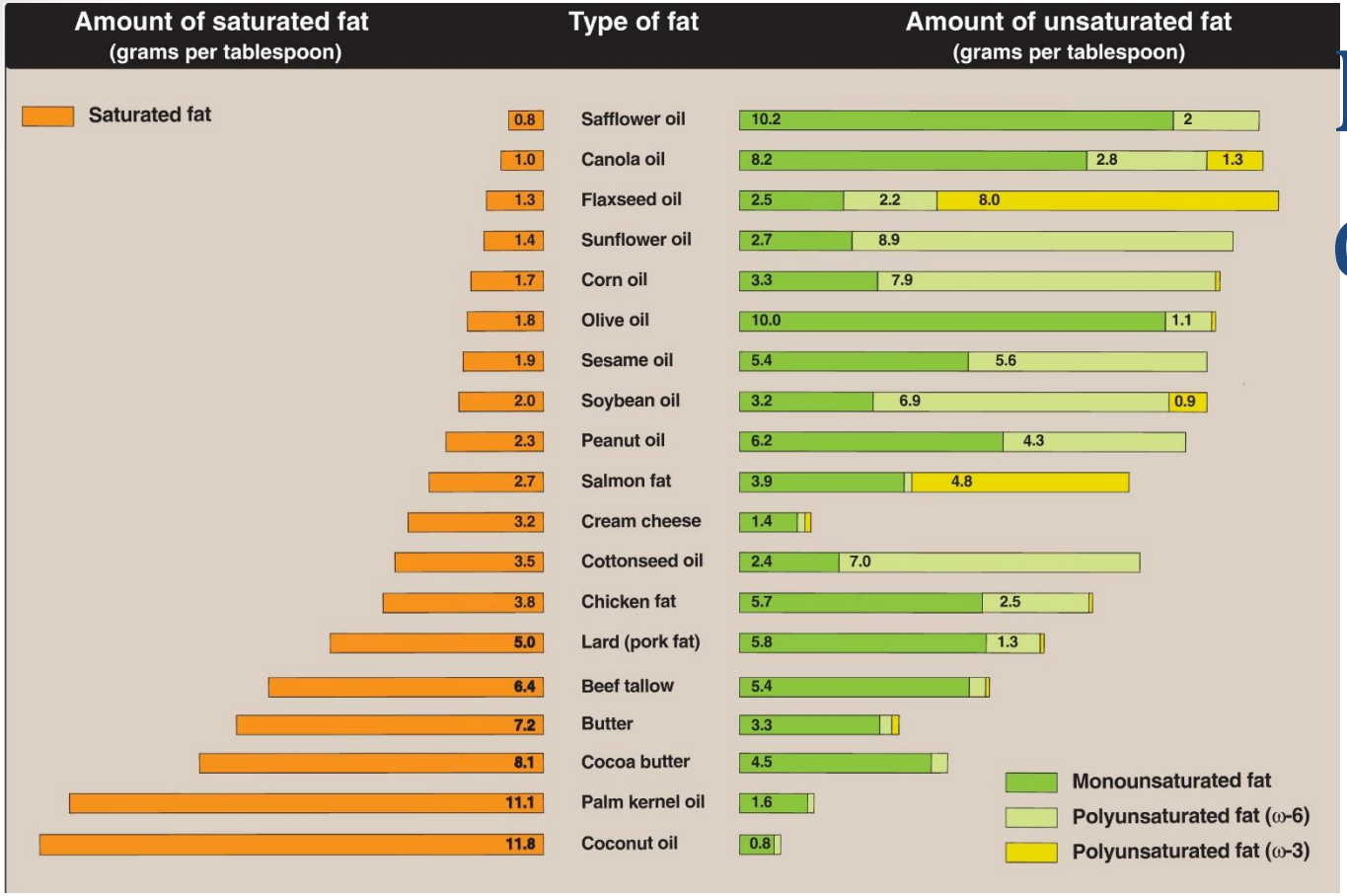
- A growing body of evidence suggests that higher levels of ω–3 polyunsaturated fatty acids provide protection against coronary heart disease.

The recommended dietary allowance

Nutrient	70-kg Man	55-kg Woman
Water-Soluble Vitamins		
Niacin	16 mg	14 mg
Riboflavin	1.3 mg	1.1 mg
Thiamine	1.2 mg	1.1 mg
Pyridoxine (B_6)	1.3 mg	1.3 mg
Pantothenic acid	5 mg	5 mg
Biotin	30 µg	30 µg
Ascorbic acid	90 mg	75 mg
Folic acid	400 µg	400 µg
Cobalamin (B_{12})	2.4 µg	2.4 µg
Fat-Soluble Vitamins		
Vitamin A	900 µg	700 µg
Vitamin D	15 µg	15 µg
Vitamin K	120 µg	90 µg
Vitamin E	15 mg	15 mg
Macrominerals		
Sodium	1.5 g	1.5 g
Potassium	4.7 g	4.7 g
Calcium	1 g	1 g
Magnesium	400 mg	320 mg
Chloride	2.3 g	2.3 g
Phosphate	700 mg	700 mg
Microminerals		
Iron	8 mg	18 mg
Copper	900 µg	900 µg
Zinc	11 mg	8 mg
Manganese	2.3 mg	1.8 mg
Molybdenum	45 µg	45 µg
Chromium	35 µg	25 µg
Selenium	55 µg	55 µg
Iodide	150 µg	150 µg
Fluoride	4 mg	3 mg

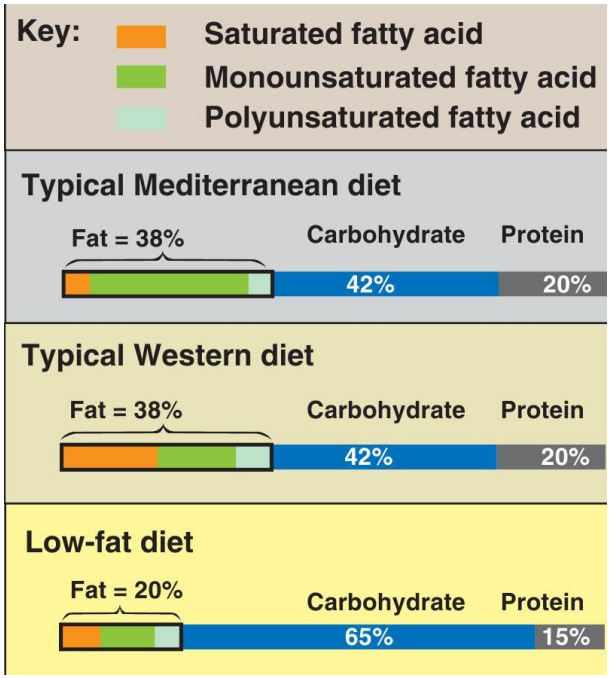
The **recommended dietary allowance (RDA)** of each nutrient, also labeled as **dietary reference intake (DRI),** is published by the Food and Nutrition Board of the National Academy of Sciences in the United States and by similar agencies in other countries. The RDA defines *a dietary intake that meets the requirements of 97.5% of healthy individuals in a category.*

Fat and diets



- Triacylglycerols are quantitatively the most important class of dietary fats. The influence of triacylglycerols on blood lipids is determined by the chemical nature of their constituent fatty acids. The absence or presence and number of double bonds (saturated vs. mono- and polyunsaturated), the location of the double bonds (ω-6 vs ω-3), and the cis vs. trans configuration of the unsaturated fatty acids are the most important structural features that influence blood lipids.

The Mediterranean diet



- The Mediterranean diet is an example of a diet rich in monounsaturated fatty acids or MUFAs (from olive oil) and ω-3 fatty acids (from fish oils and some nuts), but low in saturated fat.
  - The composition of the Mediterranean diet in comparison with both a Western diet similar to that consumed in the United States and a typical low-fat diet.
- Contains seasonally **fresh food**, with an abundance of **plant material**, low amounts of red meat, and **olive oil** as the principal source of fat.
- The Mediterranean diet is associated with decreased serum total cholesterol and LDL cholesterol – but little change in HDL cholesterol – when compared with a typical Western diet higher in saturated fats.
- Plasma triacylglycerols are unchanged.

Effects of dietary fats

TYPE OF FAT	METABOLIC EFFECTS	EFFECTS ON DISEASE PREVENTION
Trans fatty acid	↑ LDL ↓ HDL	↑ Incidence of coronary heart disease
Saturated fatty acid	↑ LDL Little effect on HDL	↑ Incidence of coronary heart disease; may increase risk of prostate, colon cancer
Monounsaturated fatty acid	↓ LDL ↓ HDL	↓ Incidence of coronary heart disease
Polyunsaturated fatty acids ω–6	↓ LDL ↓ HDL Provide arachidonic acid which is an important precursor of prostaglandins and leukotrienes	↓ Incidence of coronary heart disease
Polyunsaturated fatty acids ω–3	Little effect on LDL Little effect on HDL Suppress cardiac arrhythmias, reduce serum triacylglycerols, decrease the tendency for thrombosis, lower blood pressure	↓ Incidence of coronary heart disease ↓ Risk of sudden cardiac death

Nutrition: Biochemical aspects

- This discipline includes concepts such as chemistry and physiology of nutrition
- Examines in detail the features of not only digestion, but especially the metabolism of proteins, carbohydrates and lipids
- An important place in the culture of food belongs energy metabolism.

This section examines:

- energy consumption (BMR)
  - Factors affecting the BMR and the ECR (energy consumption in rest)
- Energy consumption for physical work
  - Food and optional thermogenesis and
  - research methods for energy expenditure

Energy consumption by organs and tissues of adult

Organs and tissues	% energy expenditure
Liver	29 – biosynthesys of glucose and ketone bodies
Brain	19
Heart	10
Kidney	7
Skeletal muscles	18
Other organs and tissues	17

Assessment of the Basal Metabolic Rate (BMR) according to the equations

Harris-Benedict equation:

BMR = 655 + 9.56 × weight (kg) + 1.85 × Height (cm)- 4.68 × age (yrs) - for women

BMR= 66.5+ 13.75 × weight (kg) + 5.0 × Height (cm)-6.78 × age (yrs) - for men

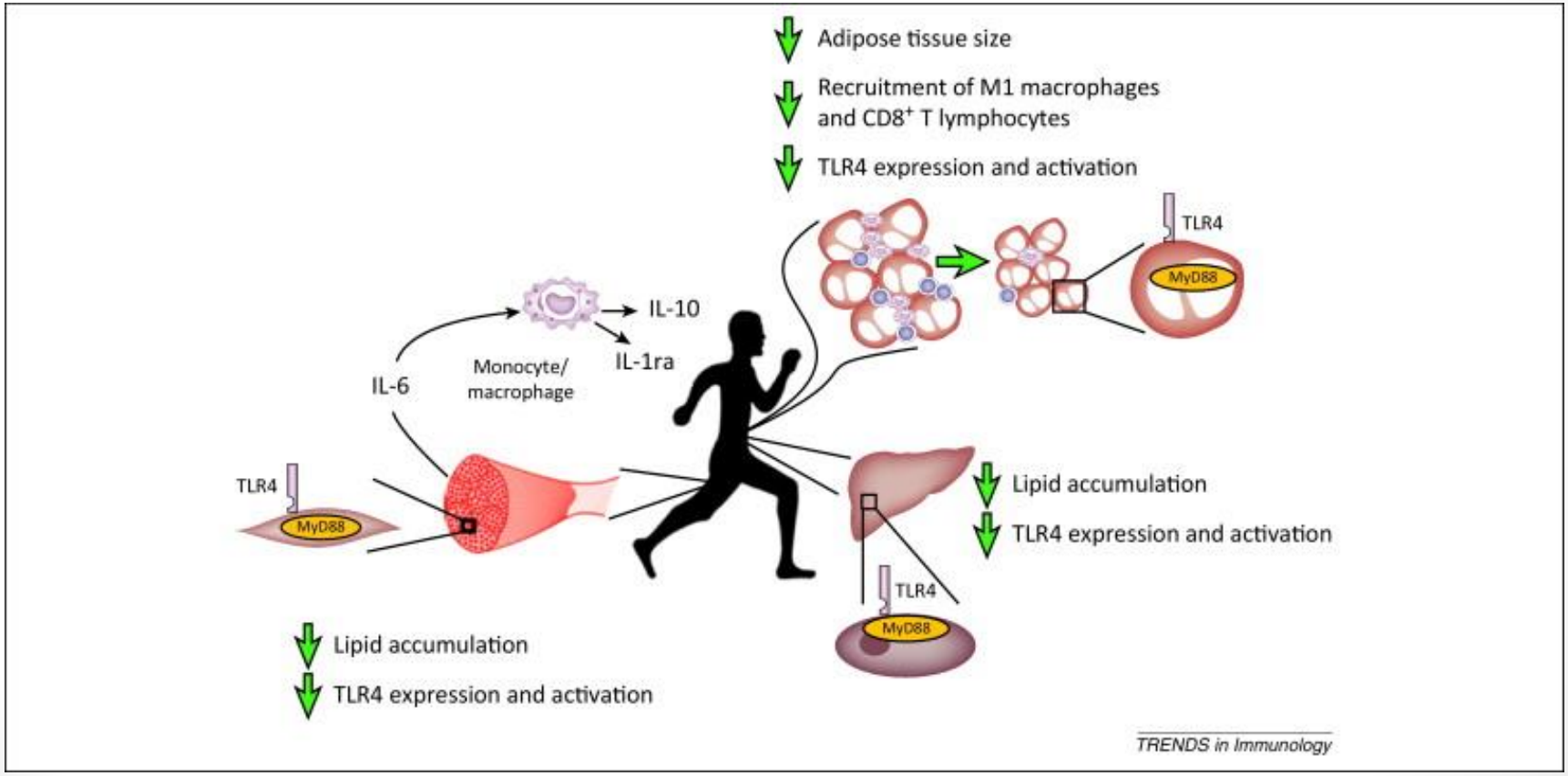
by Miffilin- St. Jeor

BMR = 10 × m (kg) + 6.25 × Height (cm) -5 × age (yrs) - 161

Quetelet index weight (kg)/height (m)^2

The range of values	evaluation
< 16.0	3rd degree of chronic energy failure
16-17	2nd degree of chronic energy failure
17-18	1st degree of chronic energy failure
18.5-25.0	Norm, at least health problems
25-30	body mass excess
30-35,0	1st degree obesity
35-40.0	2nd degree obesity
> 40	3rd degree obesity

- **CFA coefficient nat the activity is the ratio energy consumption and the values of SBI or Energy consumption+ SBI / unit time**
- **CFA shows how many times energy consumption on a particular kind of work >>> energy consumption TOE per unit time**



You maybe familiar with this information, but did not pay attention:

Consumption of proteins in an amount > 1.5 g / kg - undesirable, and in amount > this values - HARMFUL !!!

The value of protein intake is expressed in three ways:

1. **the share of the total calories, which is 10-15% of total calories**
2. **for the amount of protein per 1 kg of body weight is 0.85-1.0 g / kg body weight, but not less than 0.85 g / kg**
3. **the absolute value of protein in gram per day - in different countries is different.**

Glycemic index: for glucose 100 (fructose - 105)

product	glycemic index
Glucose	100
Honey	87
Bananas	62
Orange juice	46
Apple	39
Boiled potatoes	90
Carrot	92
Potato chips	51

Section NutritionDedicated to food as a source of energy, including the concept of estimating the coefficients of the energy value of the nutrients;

balance of power

The regulation of body weight

Adaptation to the level of energy consumption

Obesity is considered as energy imbalance in the pathogenesis of disease

en

- All nutrients are divided into macro- and micronurients
- Micronutrients include vitamins and minerals, and they come in doses of micro- and milligrams.
- They are not the energy sources, but are involved in the assimilation of food, the regulation function, growth and development of the organism

All remember about kwashiorkor. But this is marginal.

Keep in mind that high 1/3 of our diet are proteins.

Essential amino acids, with a high proportion of animal protein

The dietary lipids (butter, cheese, etc.) constitute 98% TG. Therefore, lipids should add 30-33% to the total caloric intake

This group should include as its predecessors eicosanoids - Ω^3 and Ω^6

NEFA (fish, seeds, nuts, and liquid oils best)

- **Carbohydrates should provide 55-70% of the total daily diet. Bread, rolls, pasta, pure sugar, vegetables and fruits. In addition, a healthy diet is correct**
- **25 g / day of dietary fiber. They support the composition of intestinal microflora, provides intestine peristaltics, and it is the prevention from the MS, cancerogenesis, atherosclerosis.**

Nutrition science includes 45 essential nutrients, they are not synthesized in the body and must come from food.

All nutrients are divided into 6 main groups:

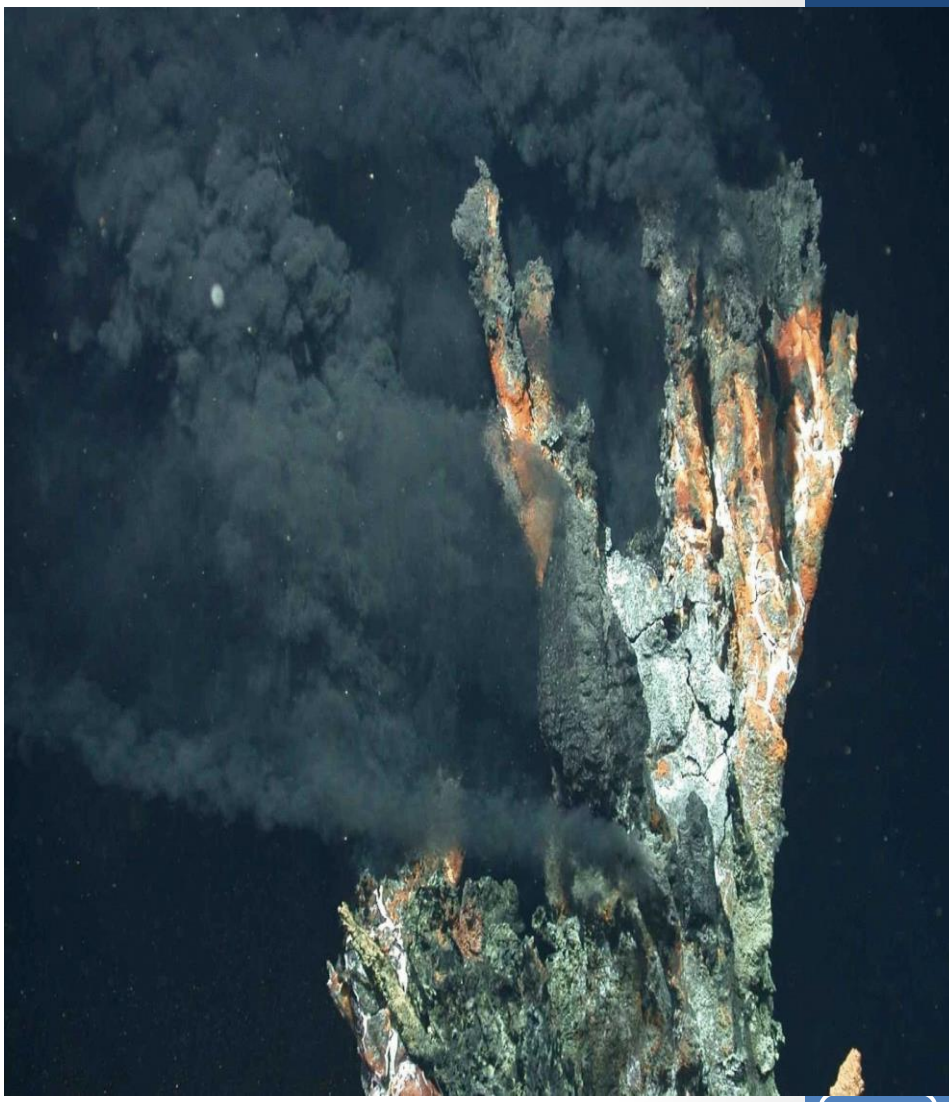
This is Proteins, Carbohydrates, Fats, Vitamins, Minerals and Water

Stocks of food in the various in-vary greatly

The longest living in the bones is Ca - 7 years, whereas amino acids disappear after a few hours of fasting.

Water tank provides cells only 4 days

- **Wars, famines, earthquakes, and et al *force majeure* are obstruction irresistible force, when disrupted the normal energy metabolism associated with the arrival of nutrients.**
- **Overeating also, like many et al pathological conditions cause the development of MS, diabetes, atherosclerosis, cancer, etc.**



Improper diet brings no less harm to human health.

The history of the development of nutrition science includes sections such as;

- **classic food, a balanced diet, adequate nutrition**
- **but always there are three main reasons:**

1. Bad quality of the food – unhealthy;

2. Eccess or lack of food

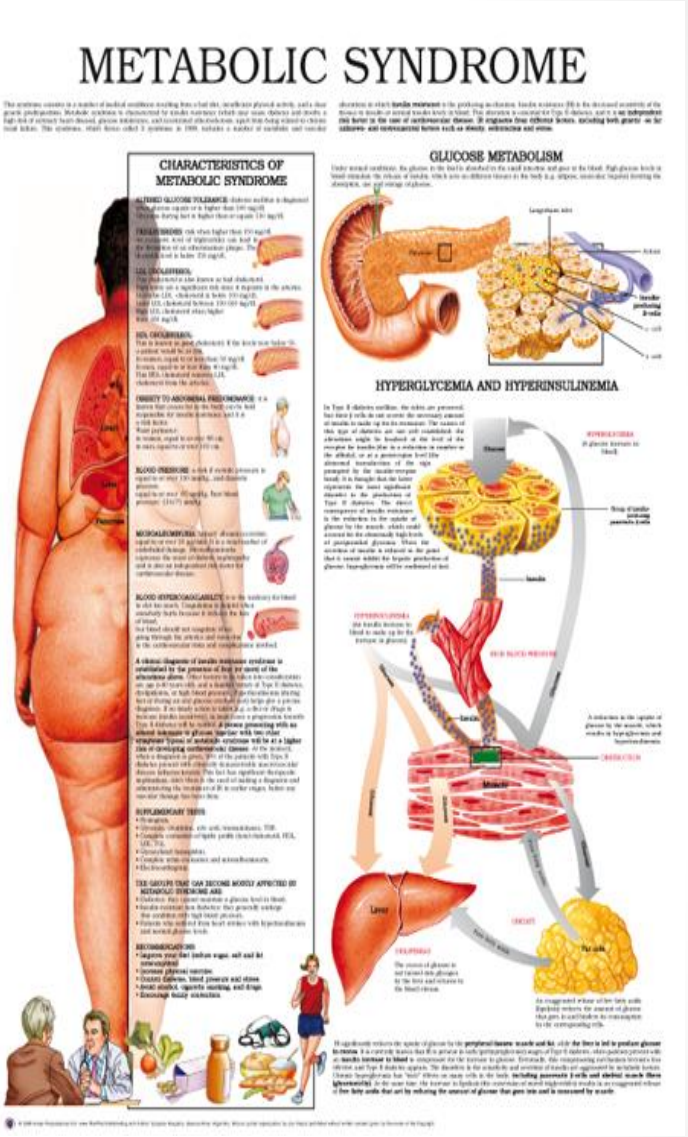
3. Improper mixing ratio in the diet

All 3 factors violate a balanced diet

Hyperlipidemias

- **Hyper-TG in its pathogenetic characteristic is divided into primary and secondary.**
- **primary hyper-TG caused by genetic disorders of metabolism LP or reinforced substrate induction (binge eating).**
- **Violation TG metabolism, which occurs as a complication main pathologic process referred to secondary hyper-TG.**
- **Primary include: family hyper-TG, familial combined hyperlipidemia, family dislipoproteinemia (type III HLP), family type hyper Chm (type I HLP).**

- **Development secondary hyper TG observed in diabetes, hypothyroidism, nephrotic syndrome, use of oral contraceptives and treatment glucocorticoids**
- **Hyper TG noted at fatty liver, in patients with acute pancreatitis**



- The result of the study total cholesterol is recommended to evaluate in conjunction with other factors, using a scale *scorpe*
  - (ESC/EAS Guidelines for the managements of dislipidemia: Atherosclerosis 2011; 21, 751; S1-S44).

- **In assessing individual risk of heart vascular lesions, the result of the study total cholesterol content . subject to interpretation in a complex of factors, primarily the the age, sex, medical history, lifestyle, systolic blood pressure, cholesterol level ratio different fractions LP.**
- **Cholesterol theory of atherosclerosis - theory of the past XX century.**
- **And it should be reevaluated.**

- atherosclerosis is common variant "metabolic pandemics" and its pathogenetic basis is deficit in polyunsaturated fatty ES cells acids
- basic cause of their low bioavailability this an excess of saturated fatty acids and primarily of palmitic acid- WITH$_{15}$H$_{31}$COOH Obtained from food poly unsaturated LCD. cells can not absorb by apo B-100 receptor endocytosis as a part of LDL.
- Everything quantity ES-poly-unsaturated LCD in ligand-free LDL is in the intima of arteries and becomes a component atheromatous the masses

- **The products that contain a large number of Palm-n-LCD $C_{15}H_{31}COOH$ is beef and manufactured out of it products, fat cow's milk and all products made from it, as well as vegetable palm butter**
- **These products contain dipalmitooleate - the undesirable for our component cells**

- **The high cholesterol content in the blood plasma is not directly relevant to the pathogenesis of atherosclerosis, however, it remains a simple diagnostic test, which reflects violation of the LCD transfer in the intercellular environment as part of the LP and the absorption of their cells. High cholesterol levels LDL It indicates high serum levels of ES-poly LCD, esterified with MS. How big is the blood level of LDL and XM, so reduced content of cells ES-poly-LCD.**

- **With food the body can enter up to 800 individual LCD: metabolic transformations *in vivo* undergo no more than 3 dozen.**
- **The remaining hundreds LCD are aphysiological and are subject to oxidation peroxisomes while simultaneously activation of α, β and ω oxidases without education ATP**

- **Peroxysomes also oxidize excess amount of exogenous $C_{15}H_{31}COOH$ – palmitic acid. On autocrine TX level implement biological endoecology function.**
  - **Maintaining the "purity" of cytosol cells and operably interact with mitochondria**
- **If peroxysomes strongly oxidize exogenous saturated $C_{15}H_{31}COOH$, - the person remains thin.**
- **therefore insufficient functions of peroxysomes are the cause of obesity.**

- Since the peroxysomes have not synthesize DNA and protein synthesis of enzymes occurs on ribosomes, then they are transported through the membrane under the action of TX ATP-dependent transporters.
- However peroxysomes may not maintain an active conformation of enzymes that rapidly becomes inactive.
- The diseases do not have specific symptoms.

- More than 50 biochemical reactions are catalyzed by peroxysomes, and a number of enzymes have no analogs in others. subcellular organelles.
- The most important reactions that take place wholly or partly in the peroxysomes, are fatty acids beta-oxidation, synthesis of plasmalogens, detoxication of glyoxal, methylglyoxal and amino acid catabolism.
- So with failure peroxisomal acyl-CoA oxidase in cells there will be observed long chain ($C_{20:0}$ arachidic acid) and very long-chain fatty acid ($C_{22:0}$ behenic and $C_{23:0}$ lignoceric).

Conclusion

Thank you for your attention!