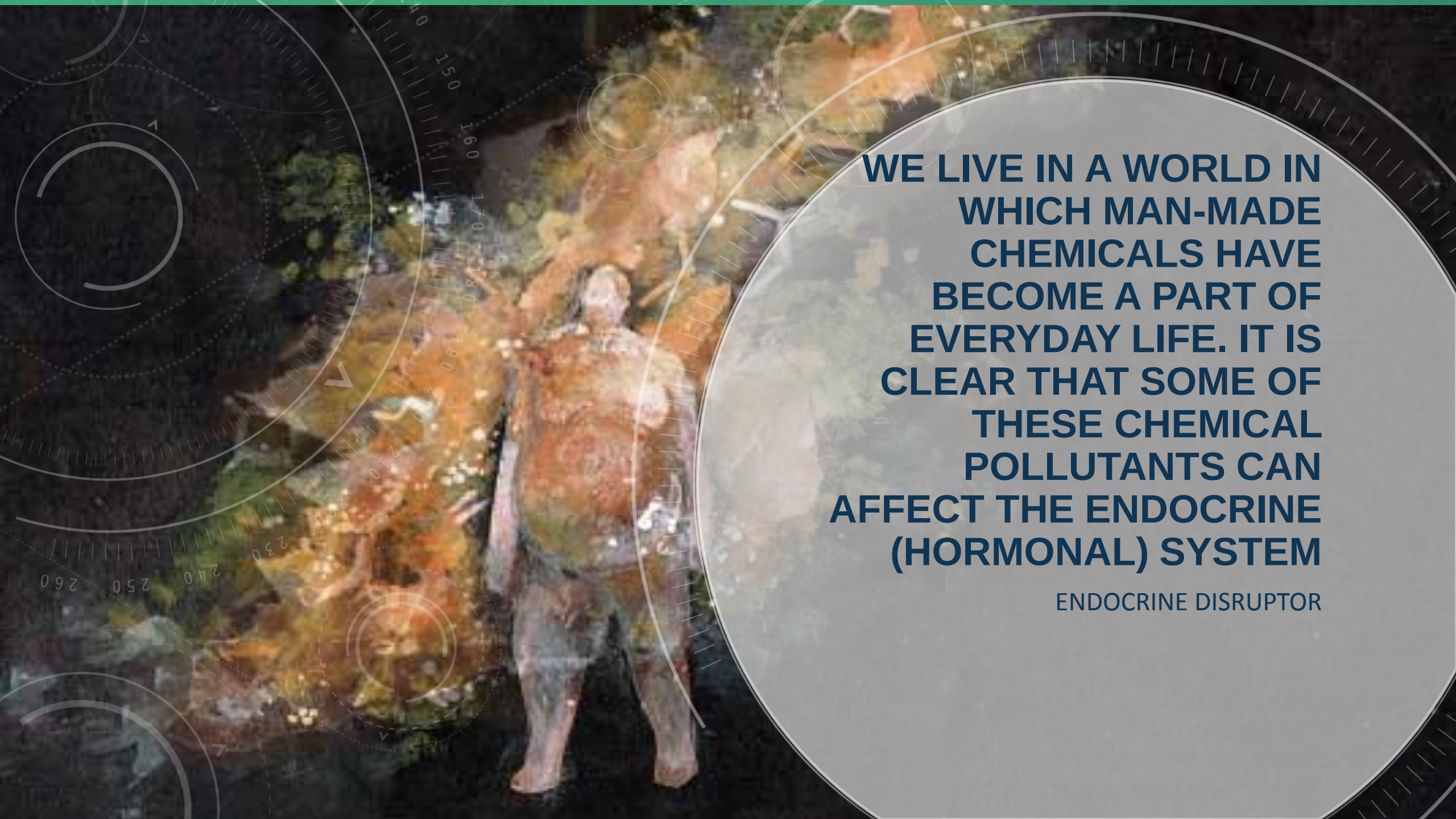
EVIDENCE THAT LINK BETWEEN EDCS EXPOSURE, OBESITY AND INSULIN RESISTANCE/DIABETES

Lynn GE-Zerbe MD, MPH
Boise Thyroid –Endocrinology, PC
Sept 13, 2017



WE LIVE IN A WORLD IN WHICH MAN-MADE CHEMICALS HAVE BECOME A PART OF EVERYDAY LIFE. IT IS CLEAR THAT SOME OF THESE CHEMICAL POLLUTANTS CAN AFFECT THE ENDOCRINE (HORMONAL) SYSTEM

ENDOCRINE DISRUPTOR

ENDOCRINE DISRUPTOR

An endocrine disruptor is an substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, its progeny, or (sub)populations.

ENDOCRINE DISRUPTOR

It is everywhere and effect everybody

TABLE 2. SOME KNOWN EDCS AND THEIR USES

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterials	Triclosan
Textiles, clothing	Perfluorochemicals

Abbreviations: BPA: bisphenol A; 2,4-D: 2,4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls

TABLE 3. EXAMPLES OF EDC ROUTES OF EXPOSURES IN HUMANS

How we are exposed to EDCs	Where the EDCs come from	EDC example(s)
Oral consumption of contaminated food or water	Industrial waste or pesticides contaminating soil or ground-water	PCBs, dioxins, perfluori-nated compounds, DDT
Oral consumption of contaminated food or water	Leaching of chemicals from food or beverage containers; pesticide residues in food or beverage	BPA, phthalates, chlorpyrifos, DDT
Contact with skin and/ or inhalation	Household furniture treated with flame retardants	BFRs
Contact with skin and/ or inhalation	Pesticides used in agriculture, homes, or for public disease vector control	DDT, chlorpyrifos, vinclozolin, pyrethroids
Intravenous	Intravenous tubing	Phthalates
Application to skin	Some cosmetics, personal care products, anti-bacterials, sunscreens, medications	Phthalates, triclosan, Para-bens, insect repellants
Biological transfer from placenta	Maternal body burden due to prior/current exposures	Numerous EDCs can cross the placenta
Biological transfer from mother's milk	Maternal body burden due to prior/current exposures	Numerous EDCs are detected in milk

Abbreviations: BFR: brominated flame retardant; BPA: bisphenol A; PCBs: polychlorinated biphenyls

Known Classes of Endocrine Disruptors

• Estrogens	DES, o,p'-DDT, DEHP, bisphenol A
• Anti-estrogens	hexachloro-4-biphenylol, luteolin
• Anti-androgens	p,p'-DDE, vinclozolin
• Progestogens	norethindrone, norgestrel
• Adrenal toxins	o,p'-DDD, glycyrrhizic acid
• Thyrotoxic agents	PCBs, goitrin
• Aryl hydrocarbons	TCDD, PAH
• Pancreatic toxins	azoxyglycosides, streptozotocin
• Metals	cadmium, nickel, aluminum
• Retinoids	vitamin A analogs

ENDOCRINE DISRUPTORS

- Pesticides (herbicides, insecticides, …)
- Plasticizers
- Natural plant metabolites
- Pharmaceuticals (contraceptives, drugs,…)
- Detergents
- Chemicals from cooking & burning
- Antibiotics
- Metals

BOX 4: PHTHALATES

Phthalates are a class of plasticizers used to soften polyvinyl chloride (PVCs), add fragrance to a product, or enhance pliability in plastics and other products. Phthalates are classified as low molecular weight (3-6 carbon backbone) and high molecular weight (>6 carbon backbone), with the low molecular weight classes thought to pose the most significant health risks. Phthalates act by interfering with androgen (testosterone) production. Because androgens are critical to male development, including genital development, boys are thought to be most vulnerable to exposure. However, androgens also play important roles in females, making phthalates relevant to both sexes. Use of some phthalates has been restricted from toys since 1999 in the EU and 2008 in the US. Phthalates are found in:

- Shampoo, lotion, nail polish and other personal care products;
- Cosmetics;
- Baby products including lotion, shampoo, powders and teethers;
- Toys;
- Scented products such as candles, detergent and air fresheners;
- Automobiles (phthalates are responsible for the 'new car' smell);
- Medical equipment including tubing, blood bags, and plastics in the NICU;
- Building materials including vinyl flooring, wall paper, paint, glue and adhesives;
- Enteric coatings of pharmaceuticals;
- Art supplies including paint, clay, wax and ink.

Phthalate exposure is linked to:

- Genital abnormalities in boys;
- Reduced sperm counts;
- Decreased 'male typical' play in boys;
- Endometriosis;
- Elements of metabolic disruption including obesity.

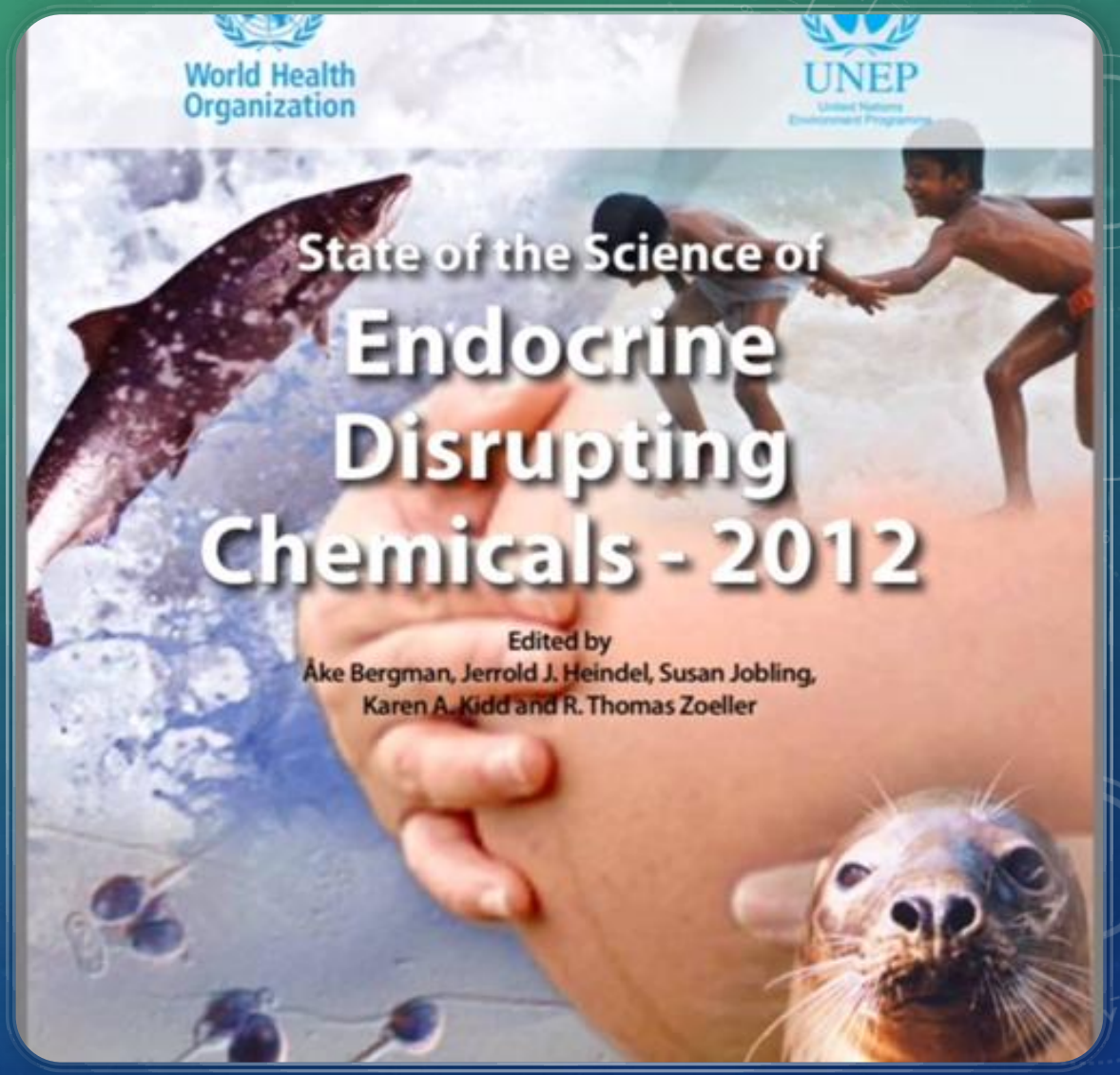
EFFECTS OF HORMONE LEVEL CHANGES

Changes in synthesis
Changes in secretion
Changes in degradation
Changes in binding proteins
Age
Gender
Developmental stage
Reproductive status
Stage of temporal rhythm


When humans are tested for the presence of EDCs in their blood, fat, urine, and other tissues, the results consistently demonstrate a variety of EDCs in all individuals worldwide.

WHO

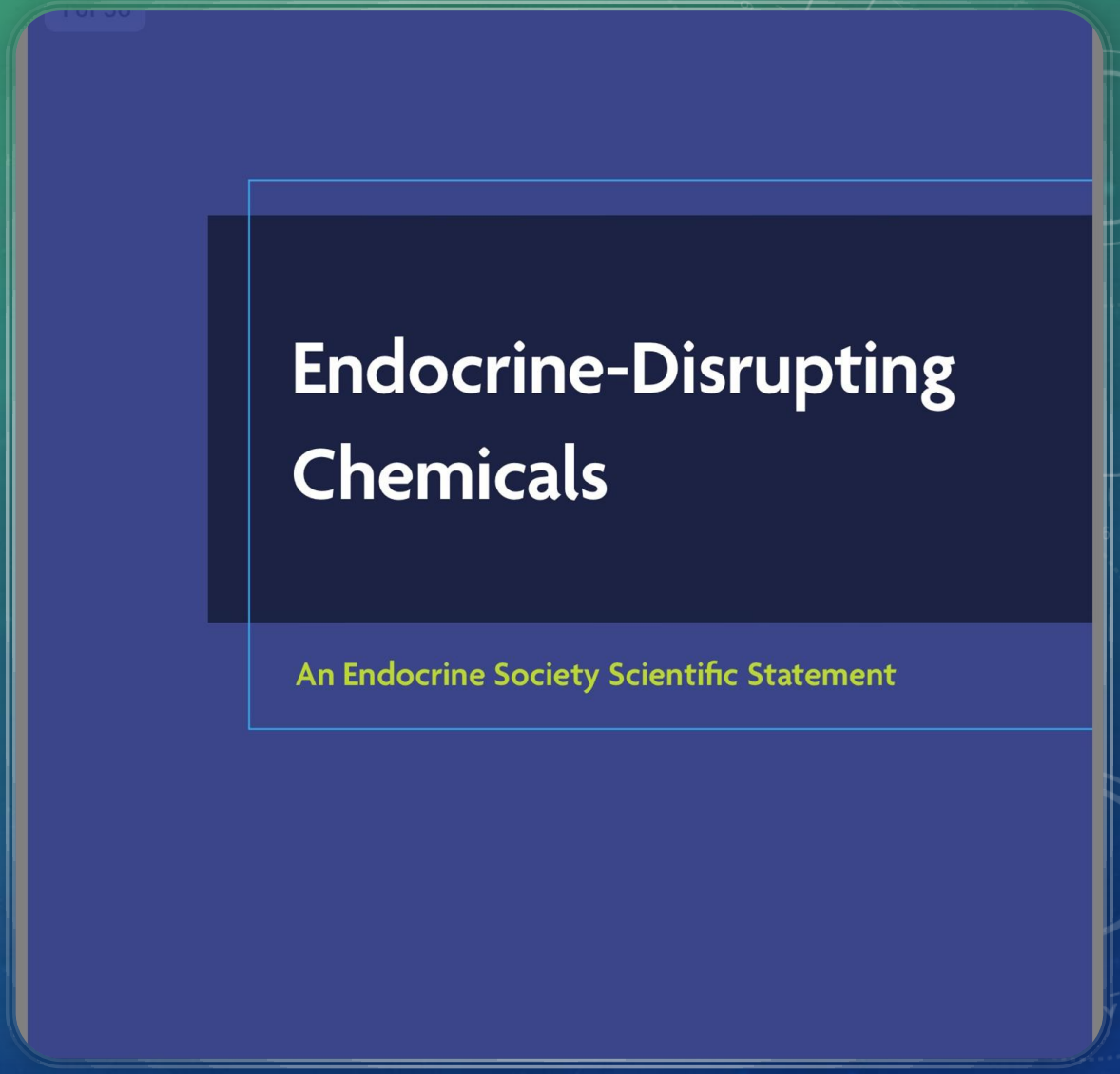
STATE OF THE SCIENCE OF ENDOCRINE DISRUPTORS



EPA

ENDOCRINE DISRUPTOR SCREENING

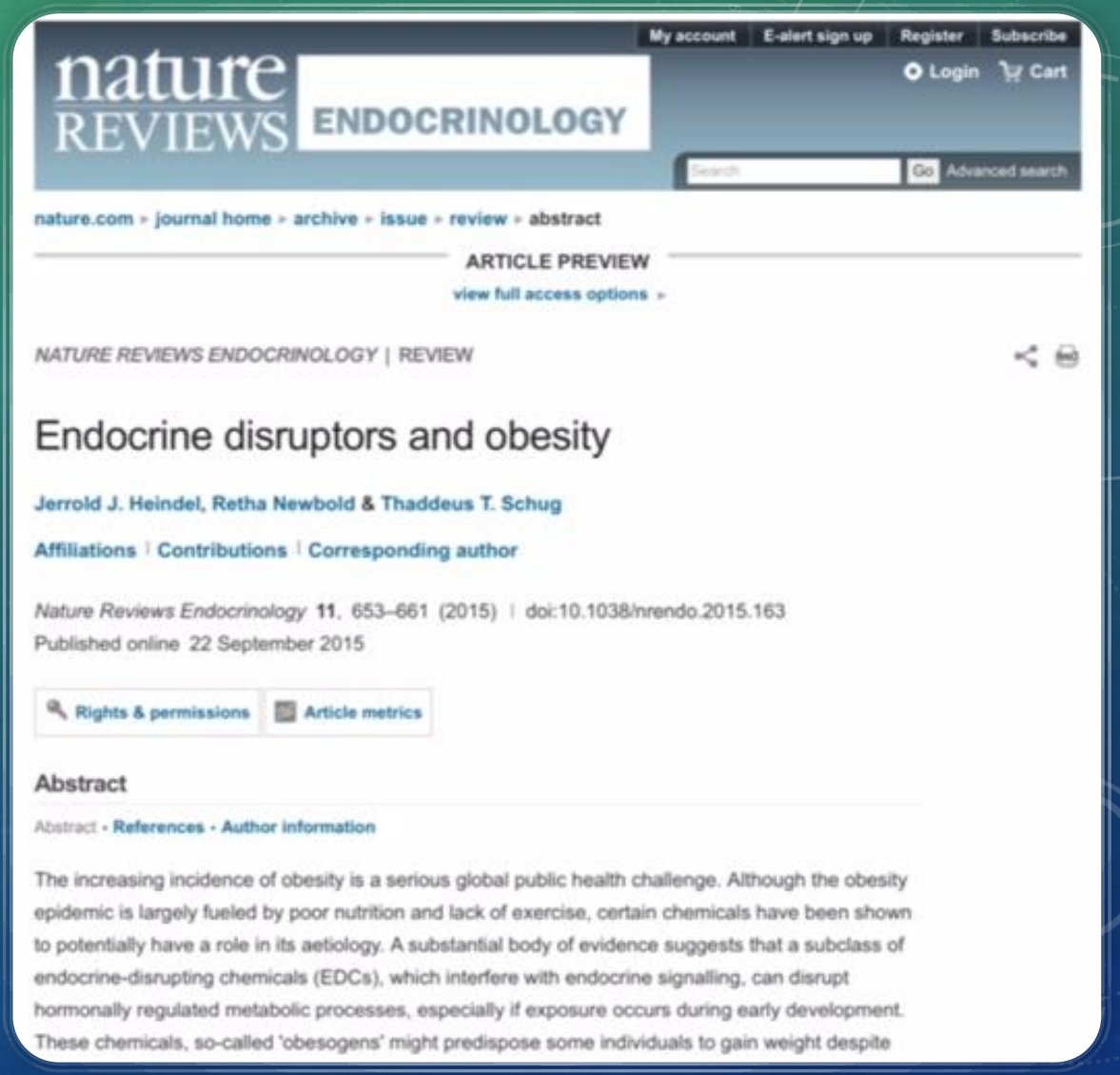
AN **ENDOCRINE SOCIETY** SCIENTIFIC STATEMENT OF EDC



NIH

ENDOCRINE DISRUPTOR DISCUSSION

NATURE REVIEW ENDOCRINE DISRUPTORES AND OBESITY



My account | E-alert sign up | Register | Subscribe

nature REVIEWS ENDOCRINOLOGY

Login | Cart

Search | Go | Advanced search

nature.com ▸ journal home ▸ archive ▸ issue ▸ review ▸ abstract

ARTICLE PREVIEW

view full access options ▸

NATURE REVIEWS ENDOCRINOLOGY | REVIEW

Endocrine disruptors and obesity

Jerrold J. Heindel, Retha Newbold & Thaddeus T. Schug

Affiliations | Contributions | Corresponding author

Nature Reviews Endocrinology **11**, 653–661 (2015) | doi:10.1038/nrendo.2015.163
Published online 22 September 2015

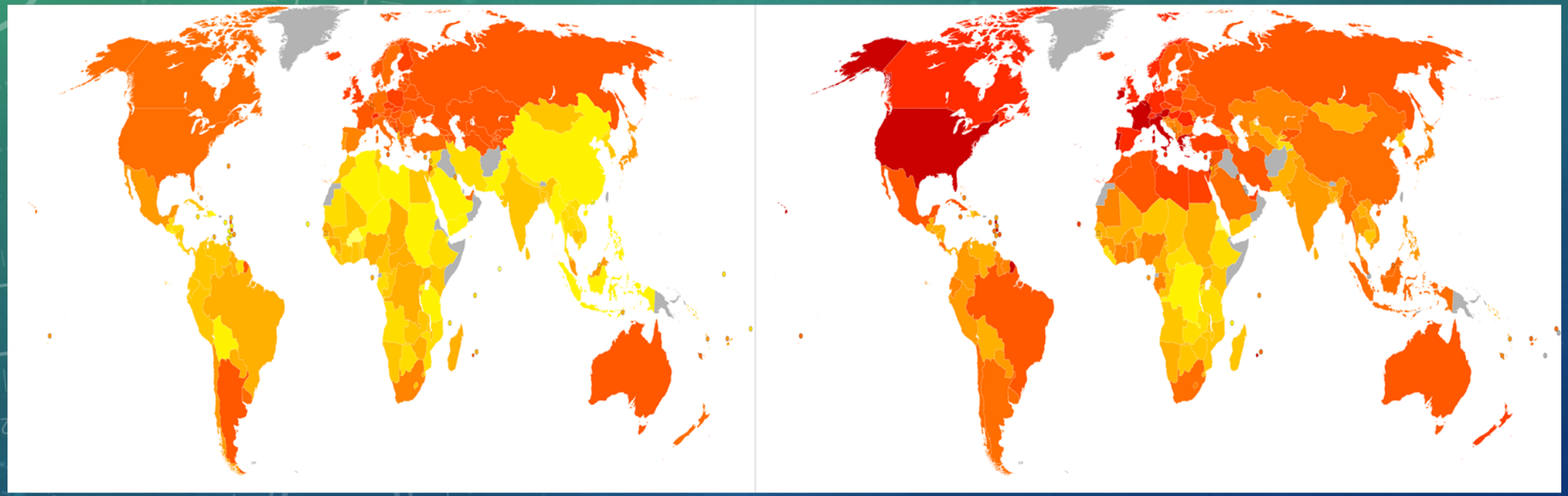
Rights & permissions | Article metrics

Abstract

Abstract · References · Author information

The increasing incidence of obesity is a serious global public health challenge. Although the obesity epidemic is largely fueled by poor nutrition and lack of exercise, certain chemicals have been shown to potentially have a role in its aetiology. A substantial body of evidence suggests that a subclass of endocrine-disrupting chemicals (EDCs), which interfere with endocrine signalling, can disrupt hormonally regulated metabolic processes, especially if exposure occurs during early development. These chemicals, so-called 'obesogens' might predispose some individuals to gain weight despite

Obesity

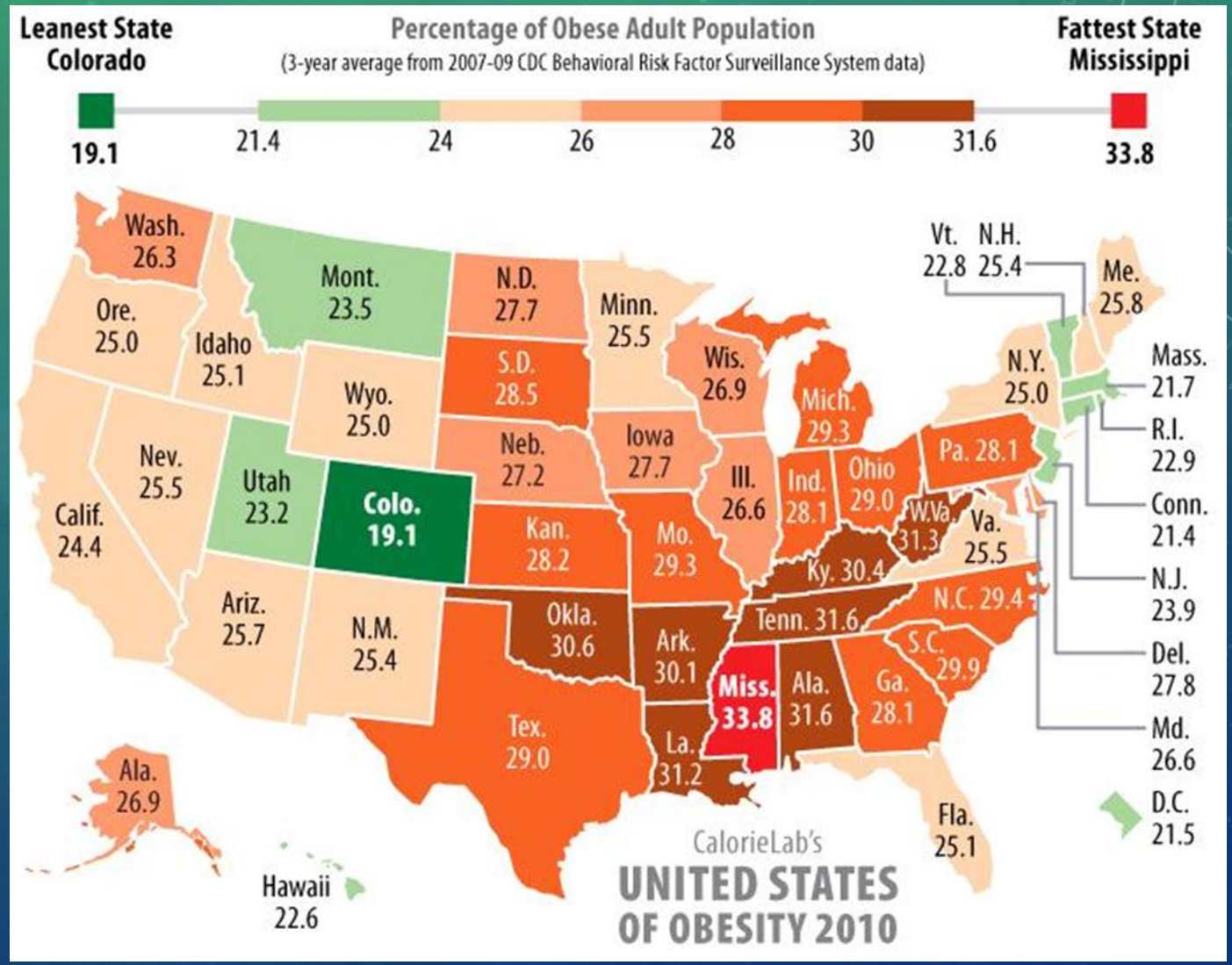


In year 1961

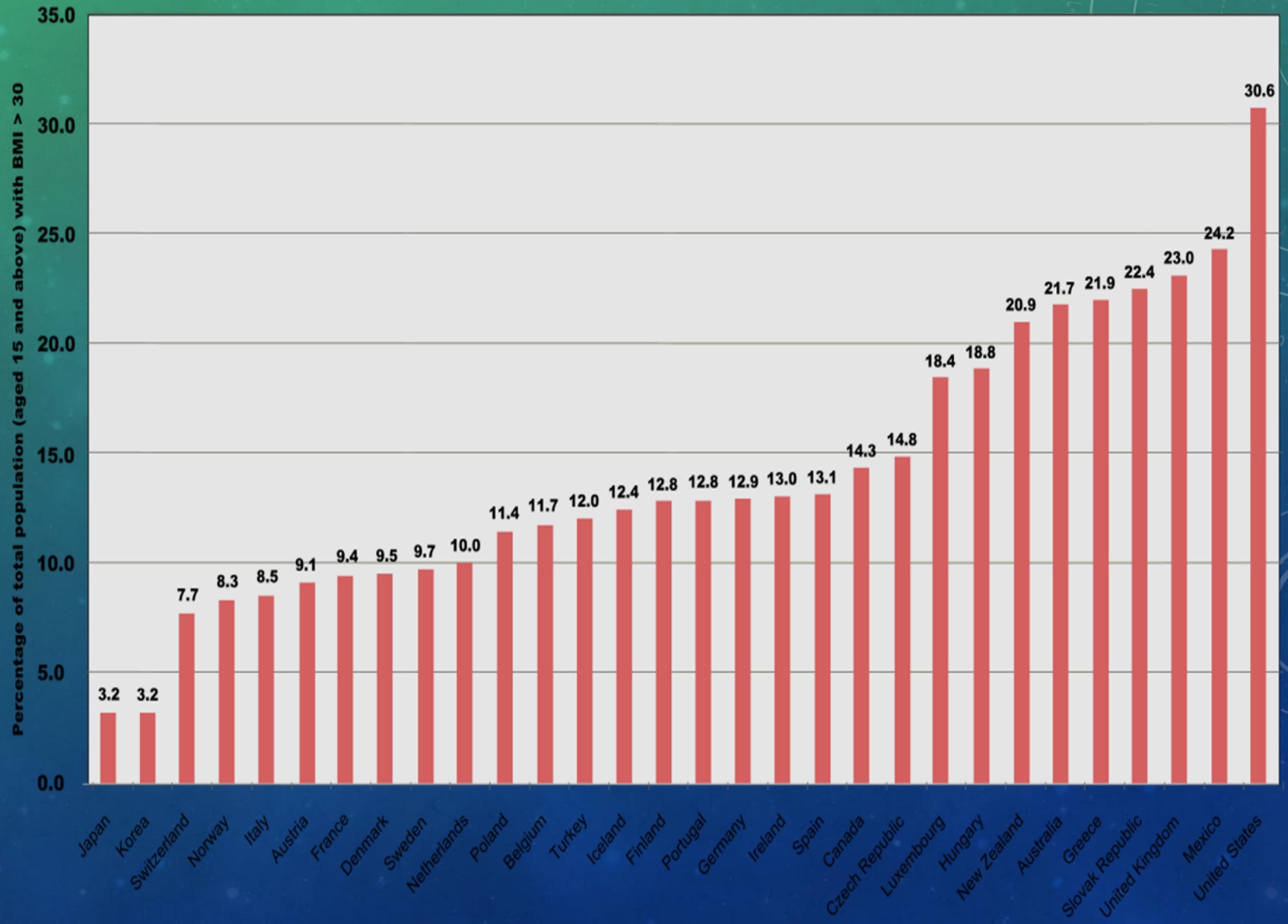
In year 2001-3

GENES

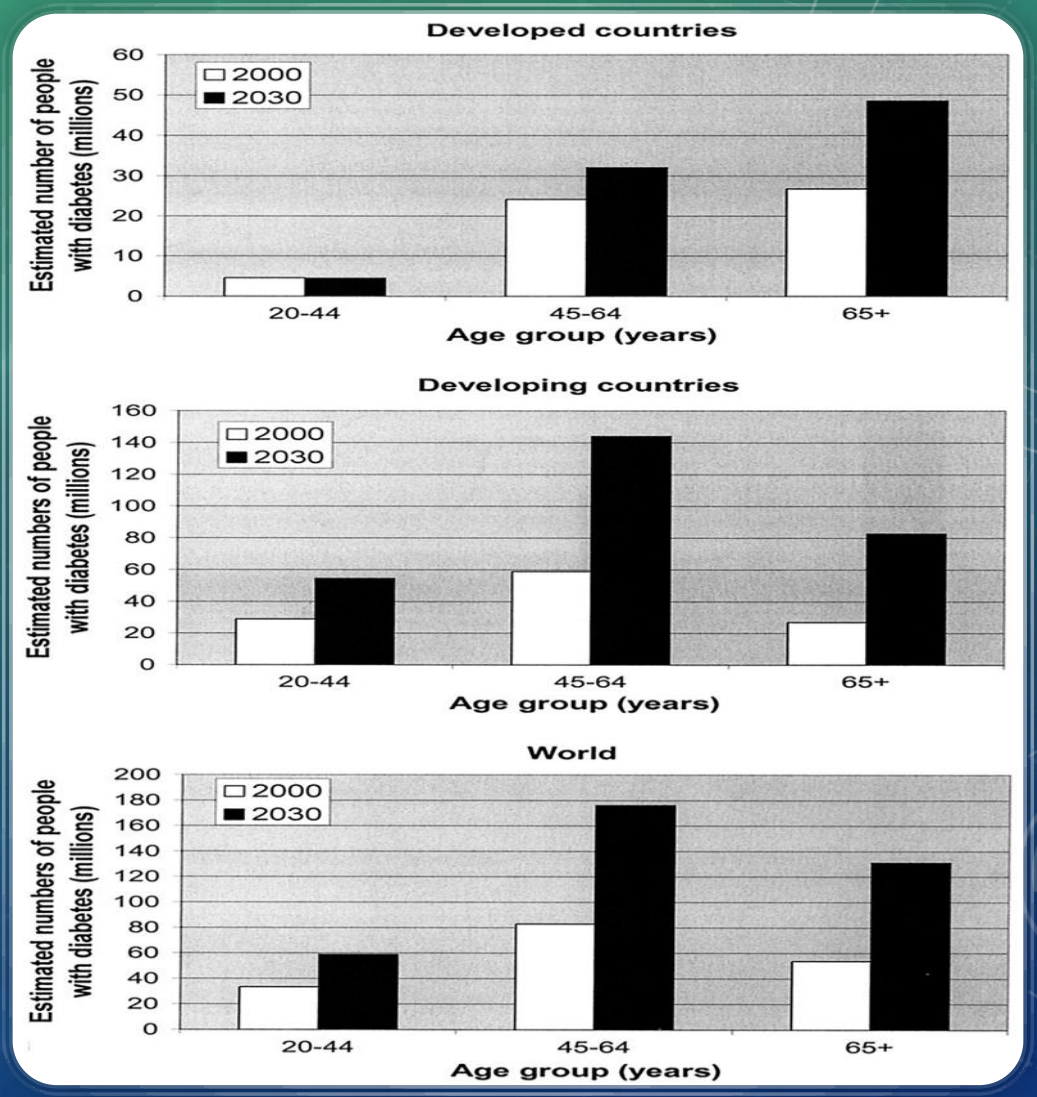
BUT NOT JUST GENES



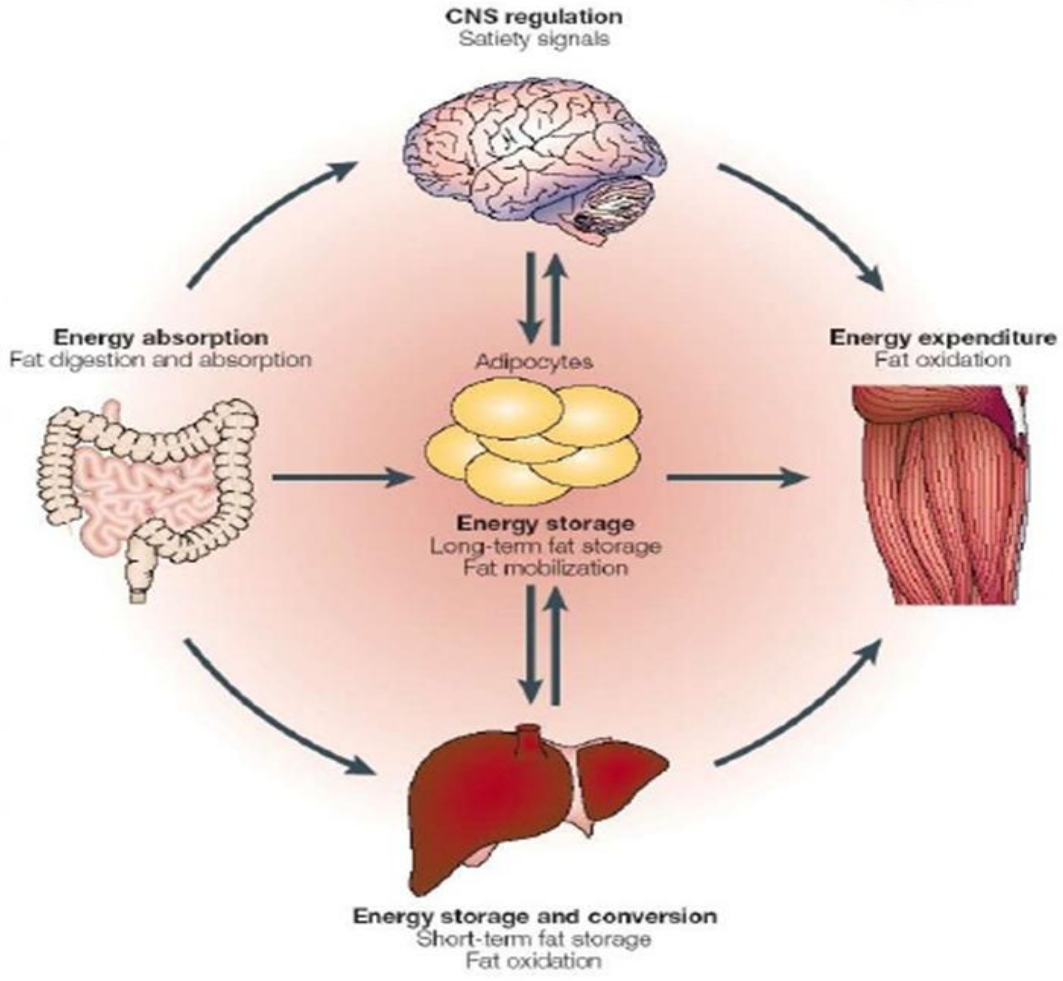
OBESITY
AROUND
WORLD



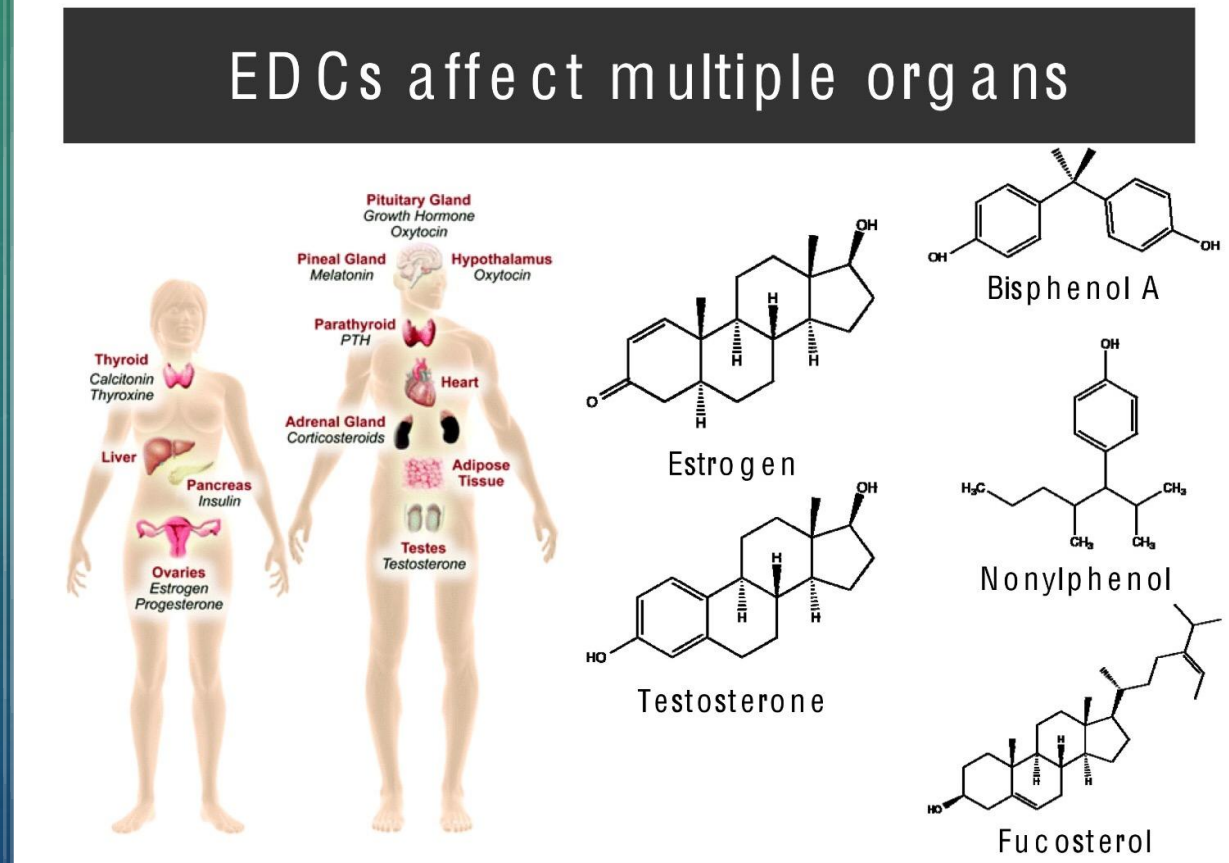
DIABETES IS EPIDEMIC EVERYWHERE



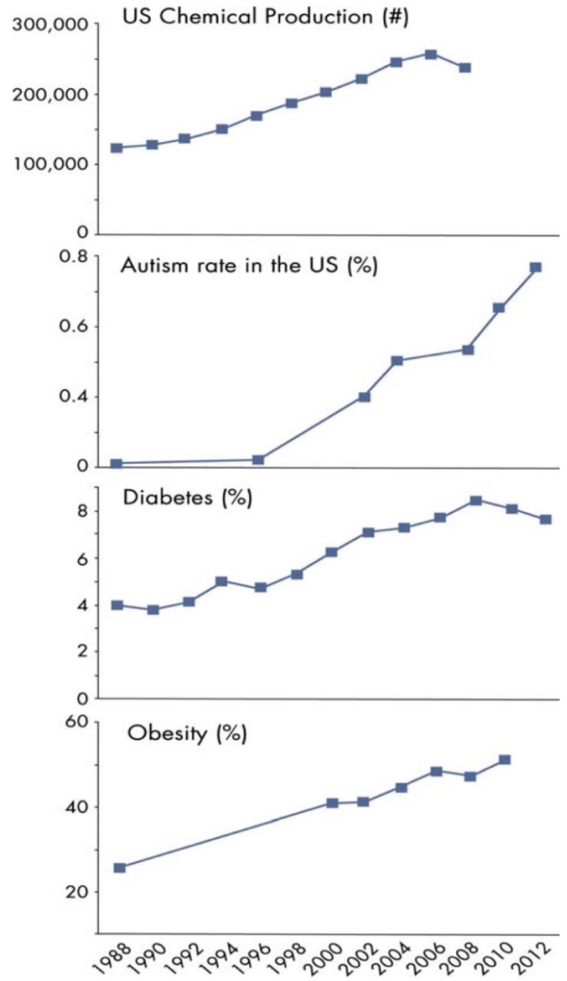
Adipocytes at the crossroads of energy homeostasis



EDC EXPOSURE



CHEMICAL PRODUCTION AND OBESITY / DIABETES

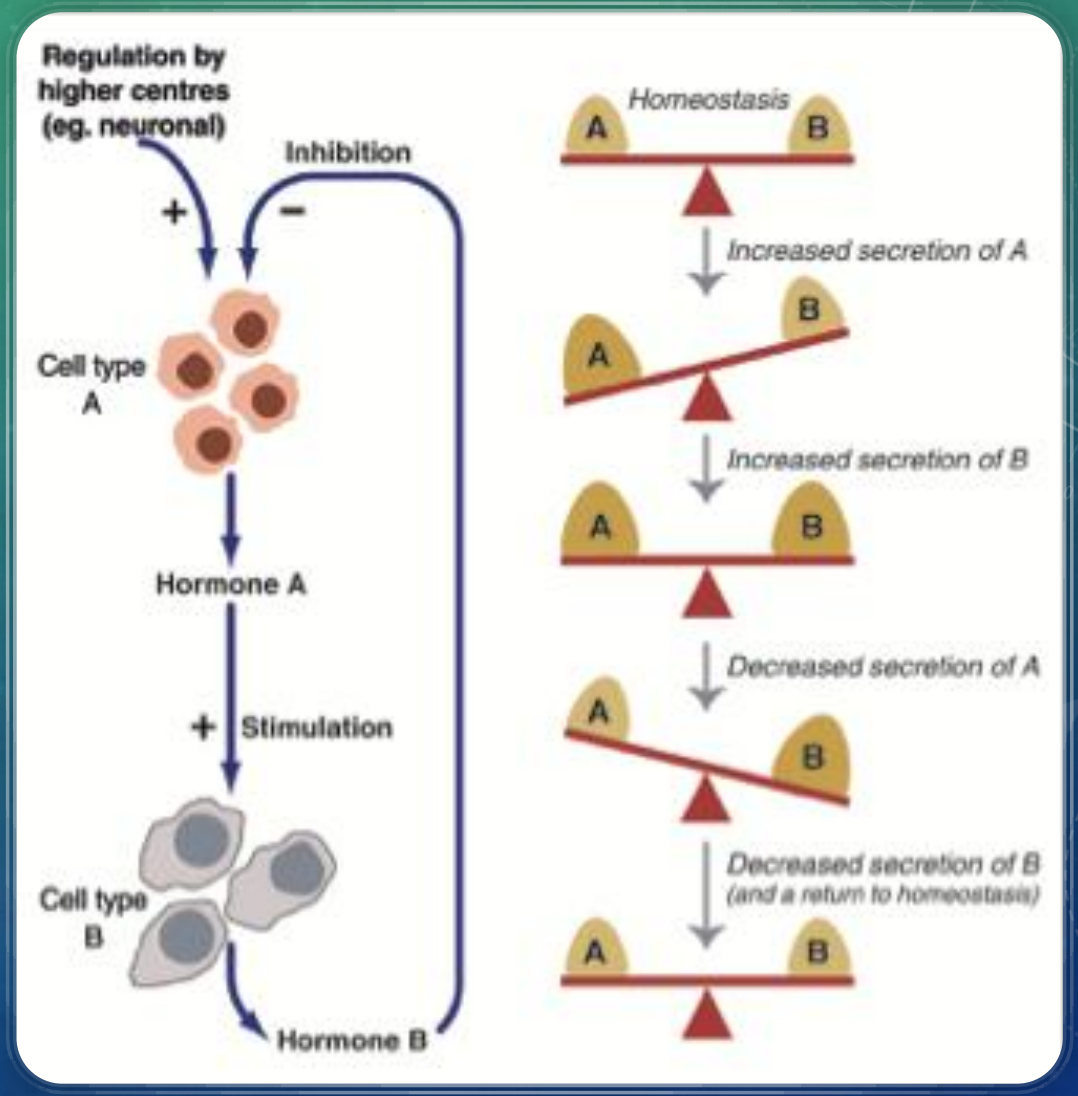


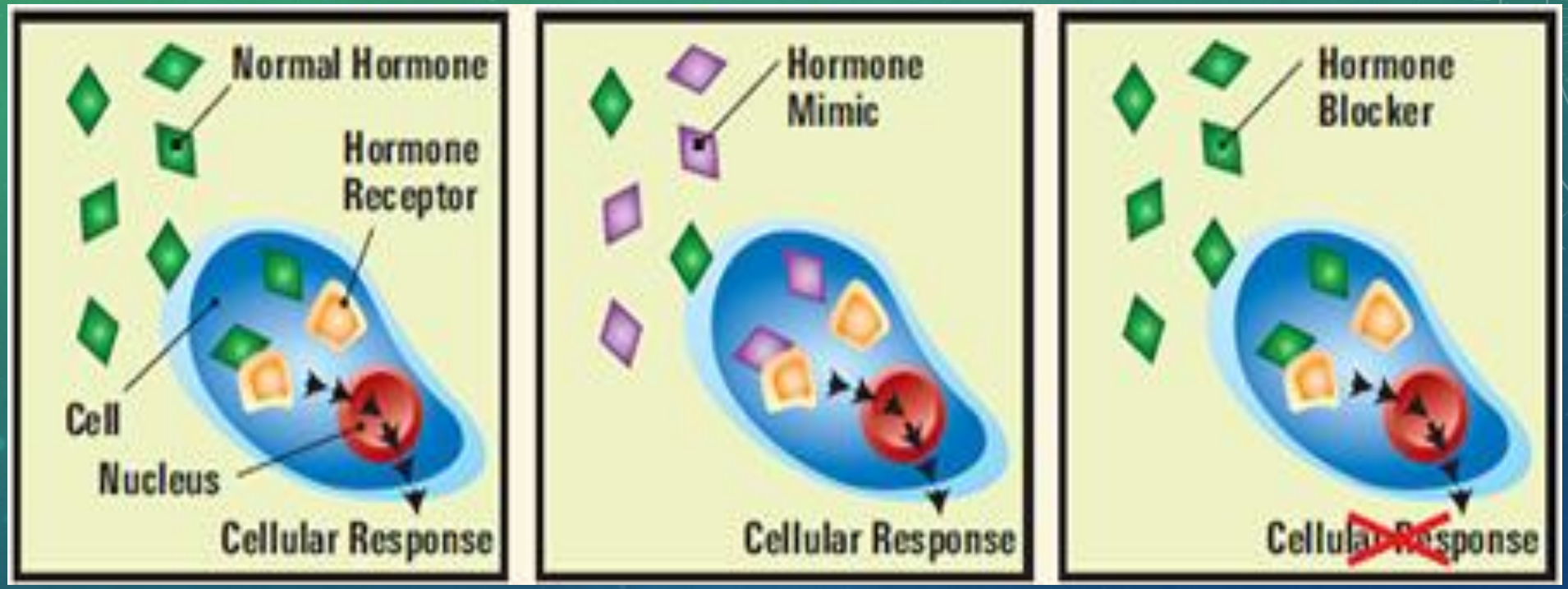
Gore et al, 2014

EDC EXPOSURE IN ANIMAL

ENDOCRINE AND PARACRINE SYSTEMS

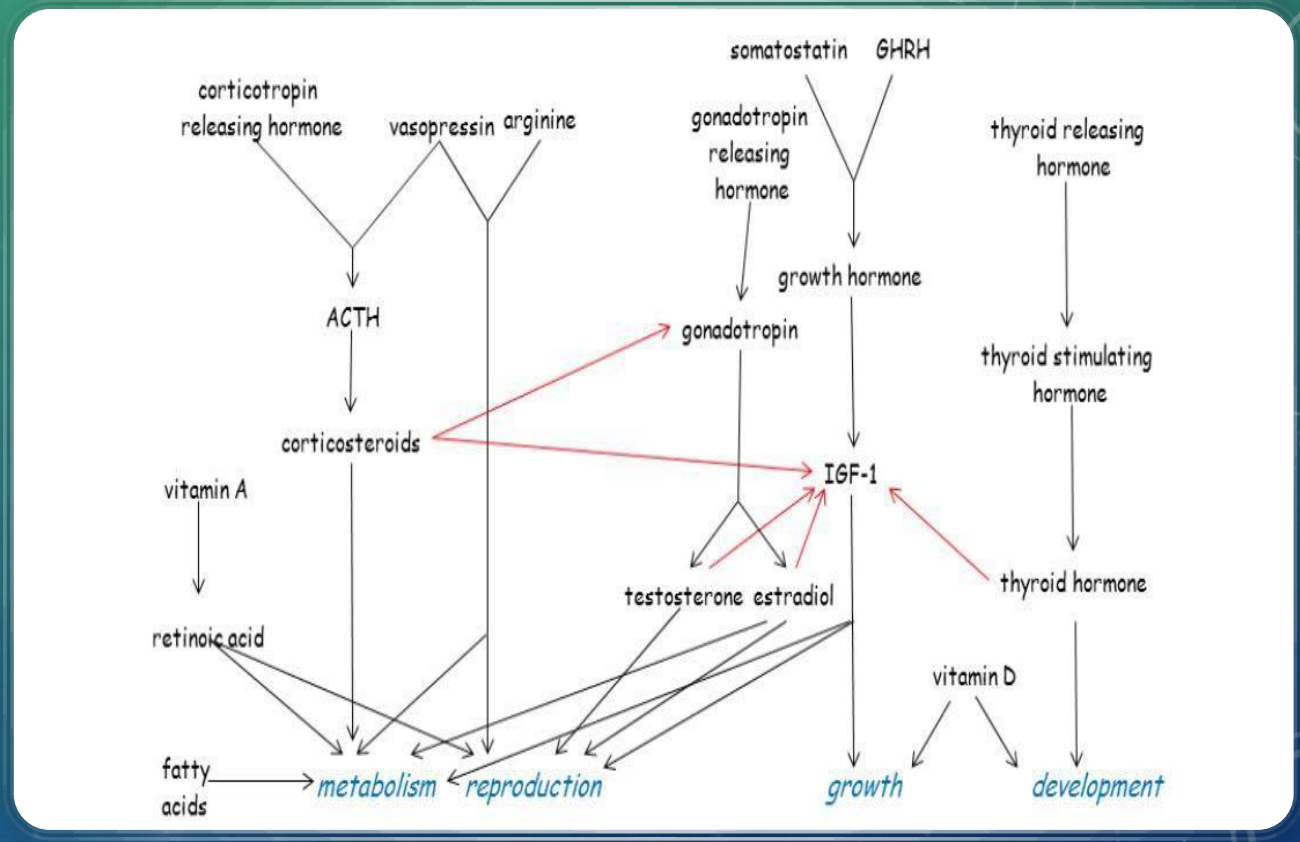
HOMEOSTASIS (NEGAGTIVE FEEDBACK SYSTEM)



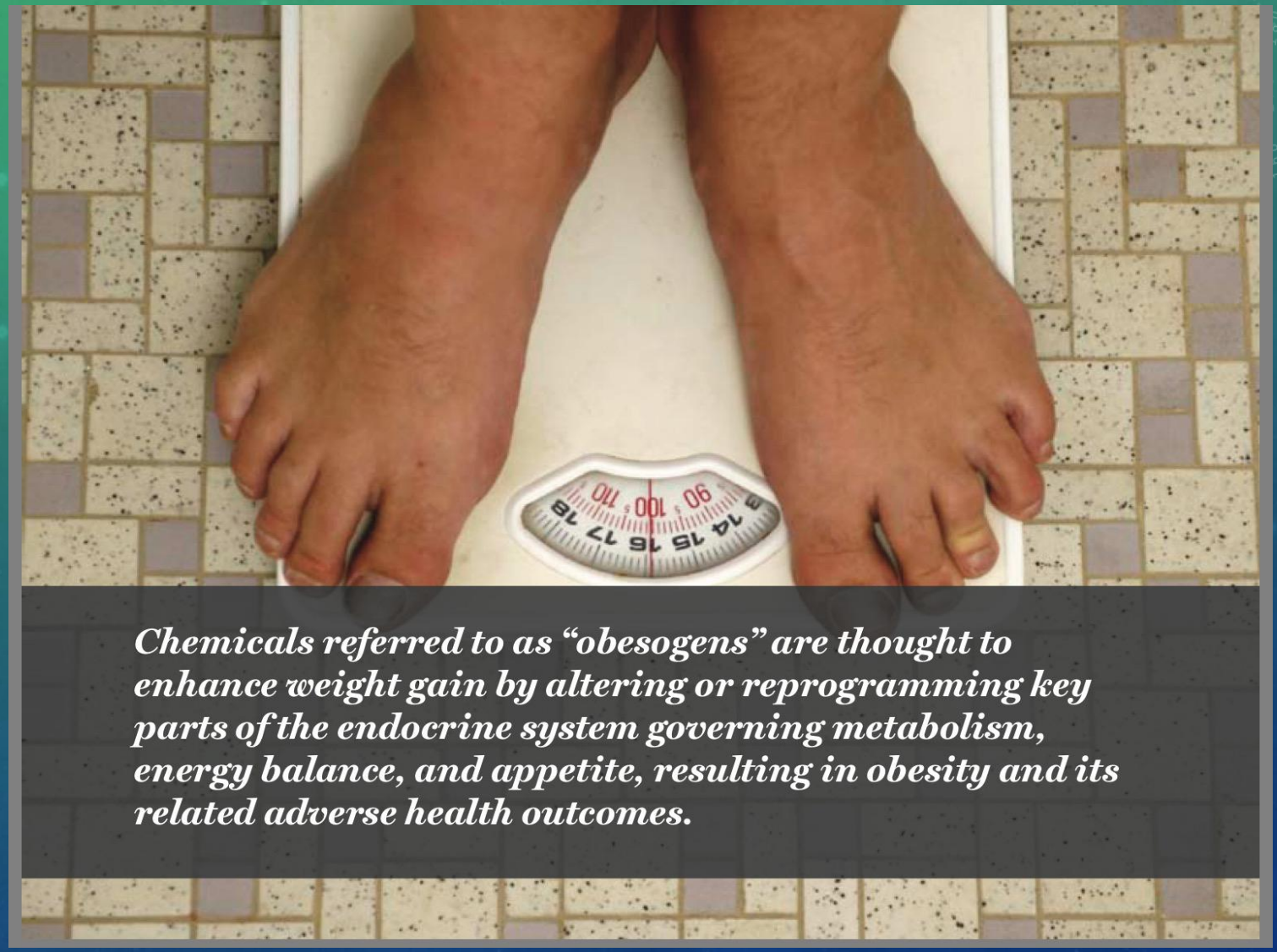


When absorbed in the body, an endocrine disruptor can decrease or increase normal hormone levels (left), mimic the body's natural hormones (middle), or alter the natural production of hormones (right) - NIH

EDC STORES IN THE FATTY TISSUE (LONG HALF LIFE)



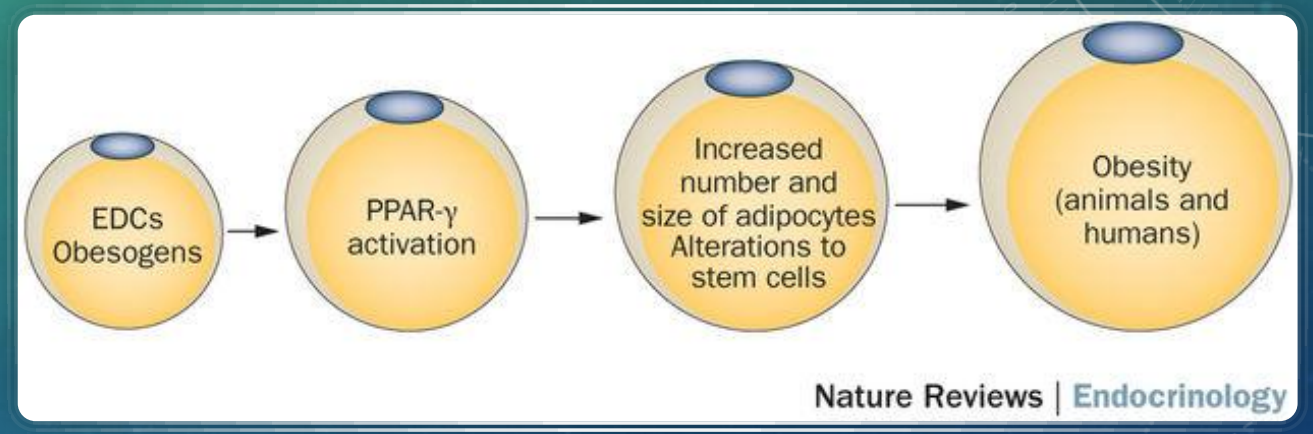
Neurontin-endocrine pathways known to be affected by EDCs resulting in symptoms of metabolic syndrome and disruptions in reproduction, growth and development



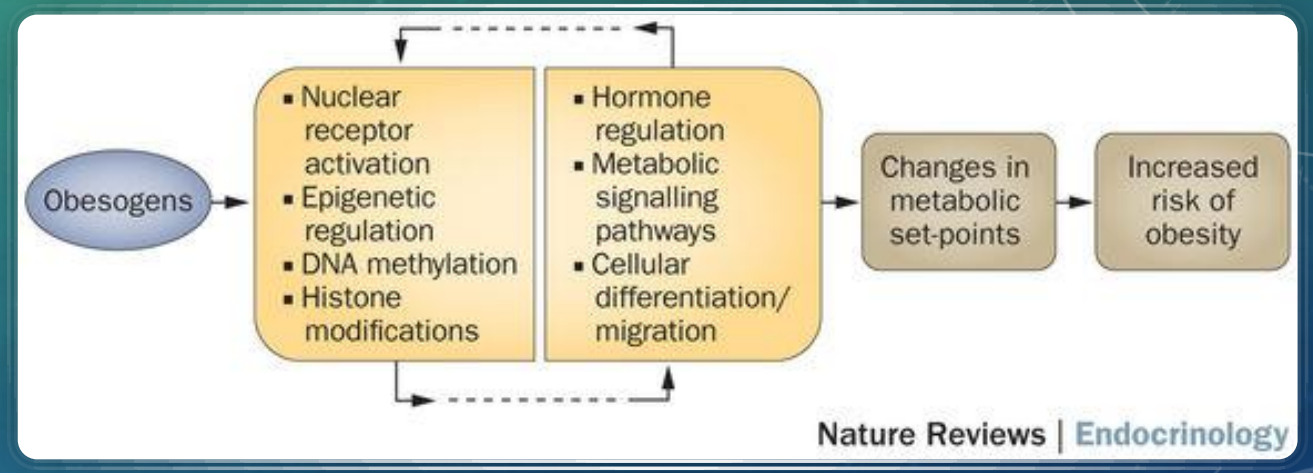
Chemicals referred to as "obesogens" are thought to enhance weight gain by altering or reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes.

OBESOGENS

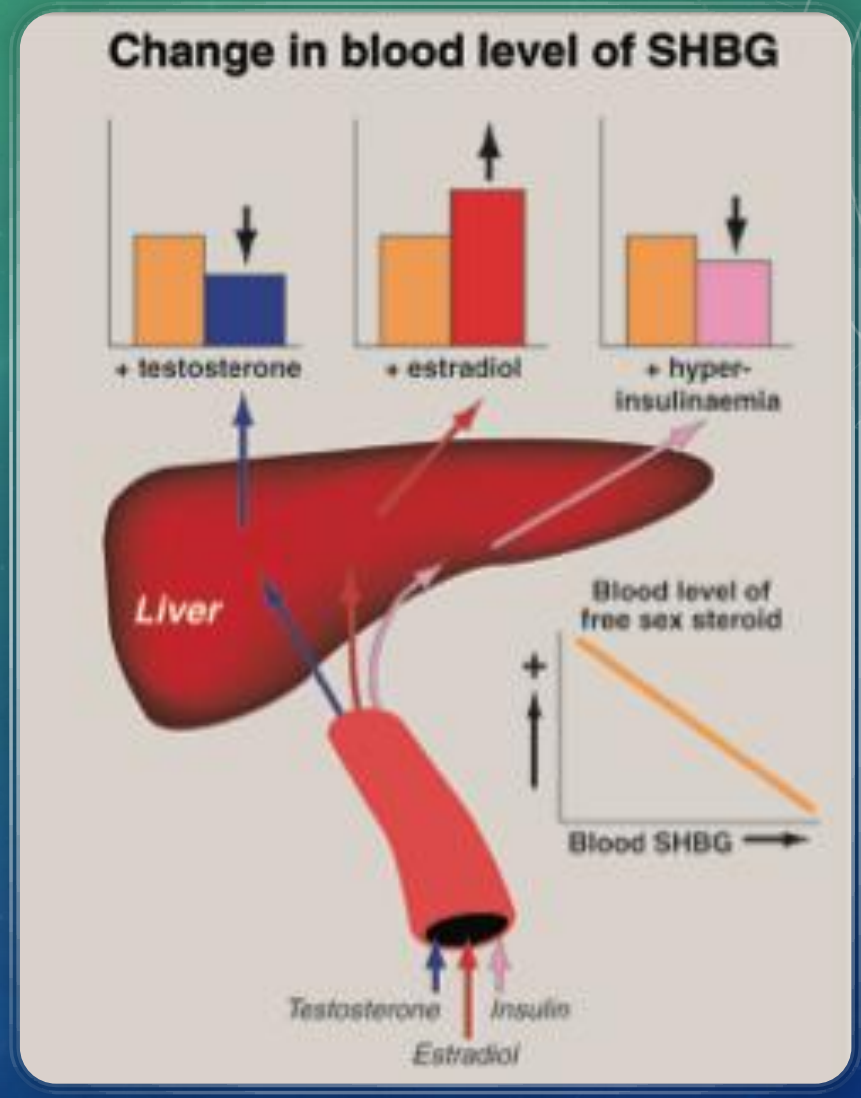
ANYTHING CAN CAUSE OBESITY



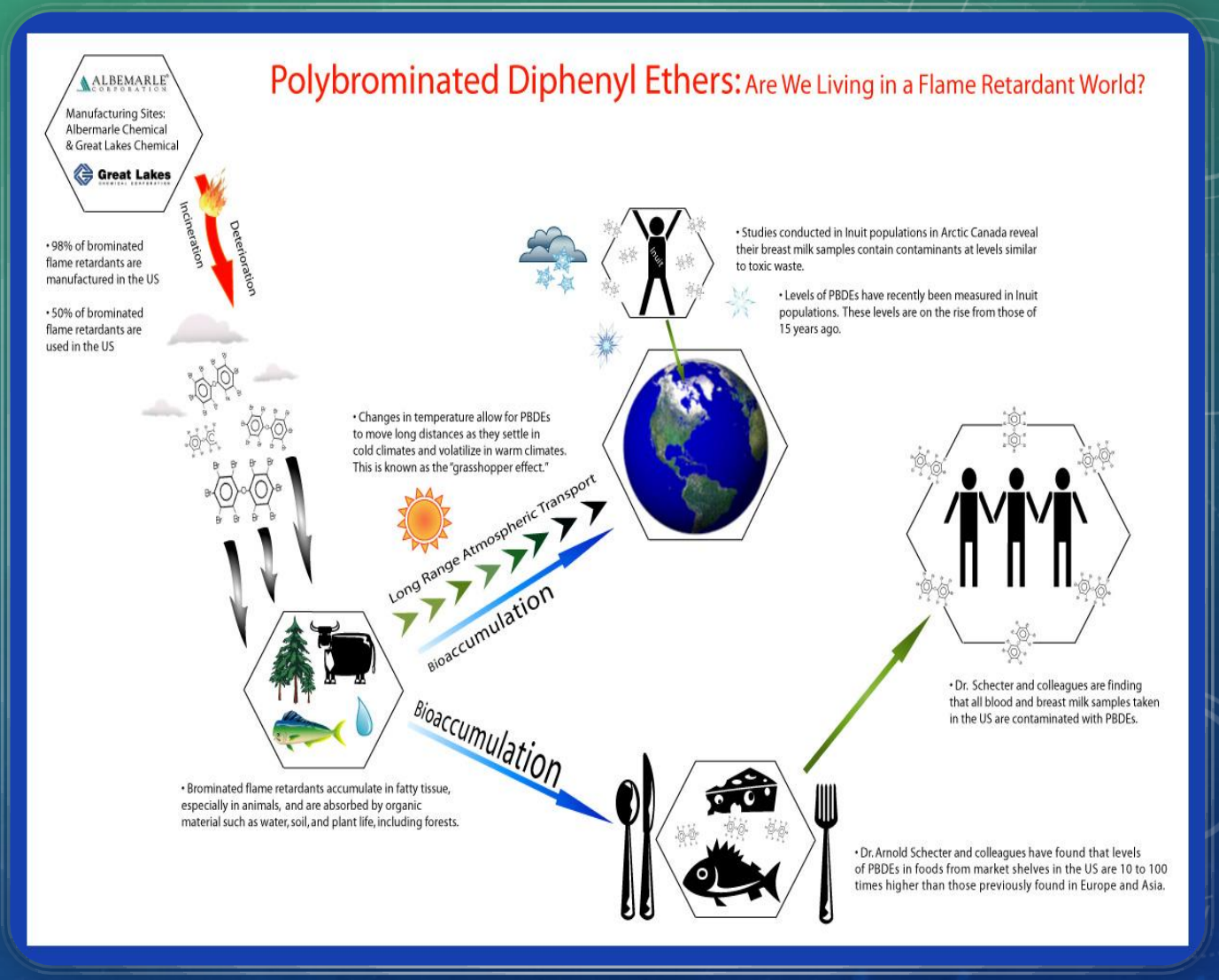
HOW IT WORKS?


Obesogens
▪ Nuclear receptor activation
▪ Epigenetic regulation
▪ DNA methylation
▪ Histone modifications
▪ Hormone regulation
▪ Metabolic signalling pathways
▪ Cellular differentiation/ migration
Changes in metabolic set-points
Increased risk of obesity
Nature Reviews | Endocrinology

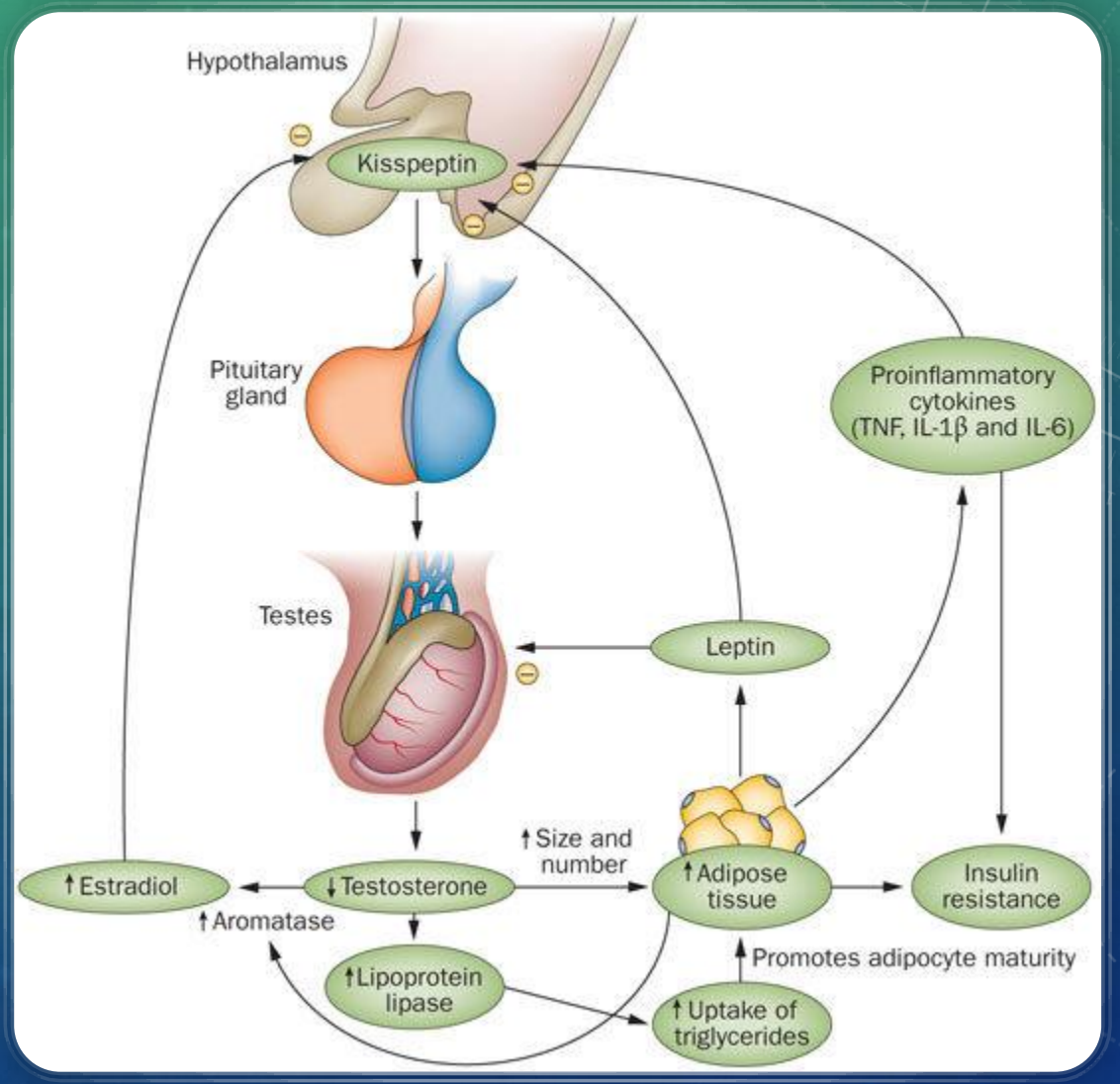
Cross talk between endocrine axes in the human with particular relevance to endocrine disruptor



FLAME RETARDANT



COMMUNICATION BETWEEN HORMONE, FATTY TISSUE, BRAIN AND CYTOKINS



WHERE IS BPA?

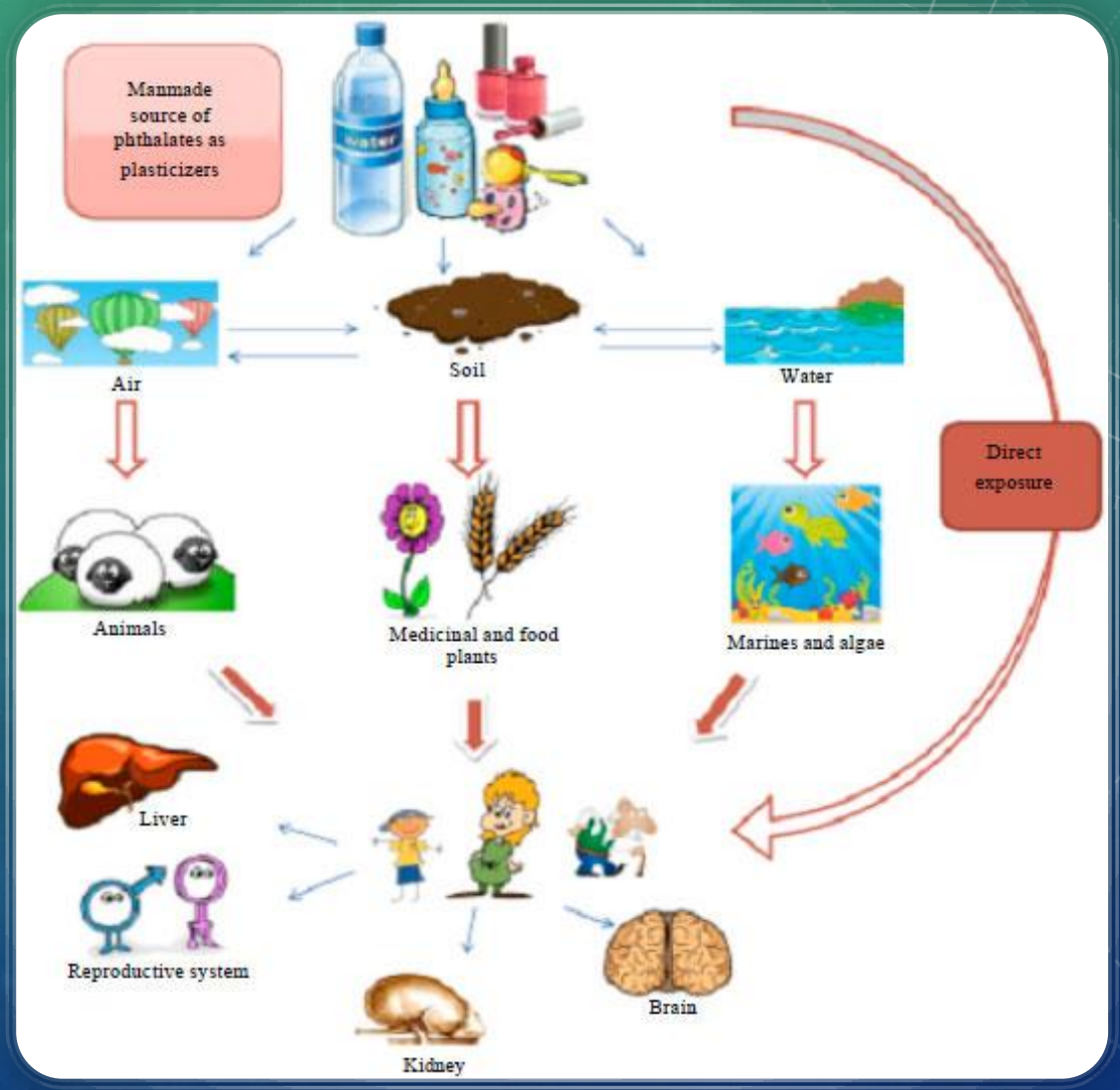
BPA is nearly ubiquitous in our society (6 billion lbs BPA manufactured/year)

- Epoxy resins: medical piping, food cans, liquid infant formula

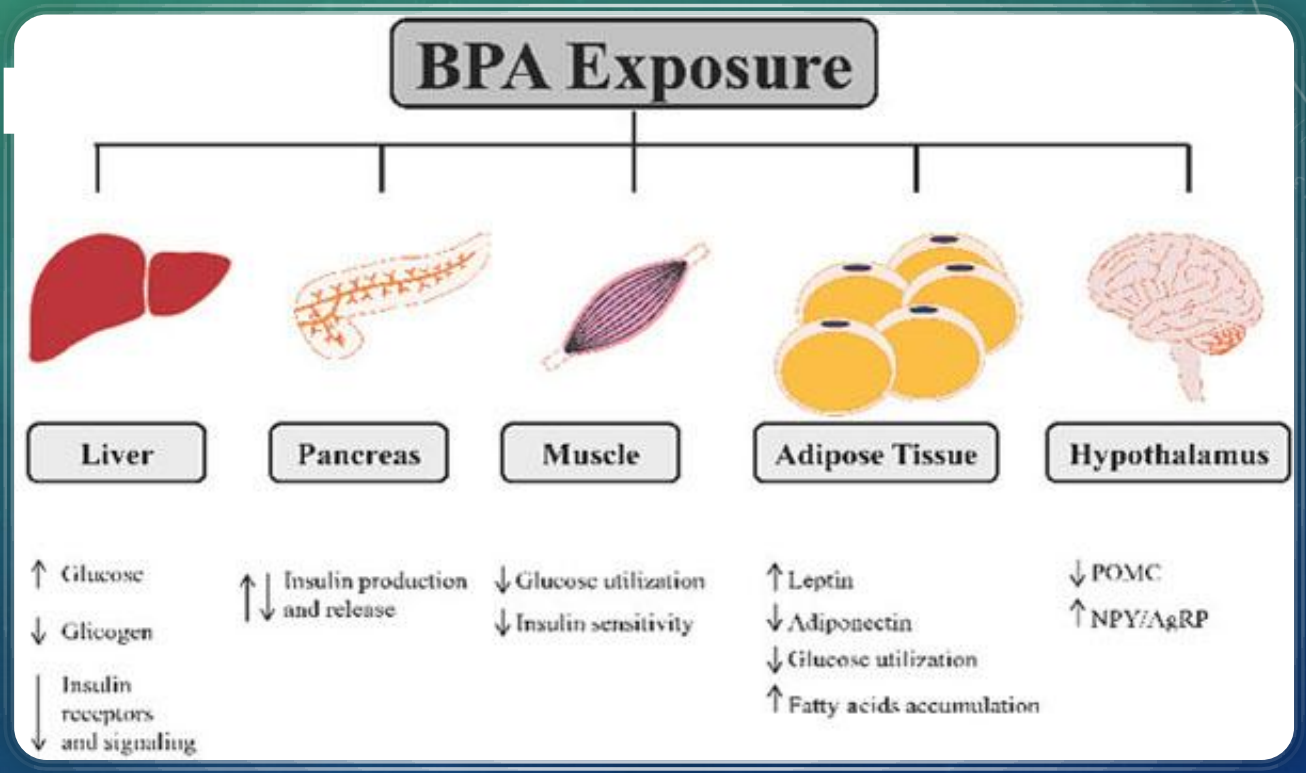
- Polycarbonate plastics: plastics #7, food containers, dental sealant, water/baby bottles

- Thermal paper: sales receipts, cigarette filters, lottery tickets, recycled paper products

WHERE IS BPA?

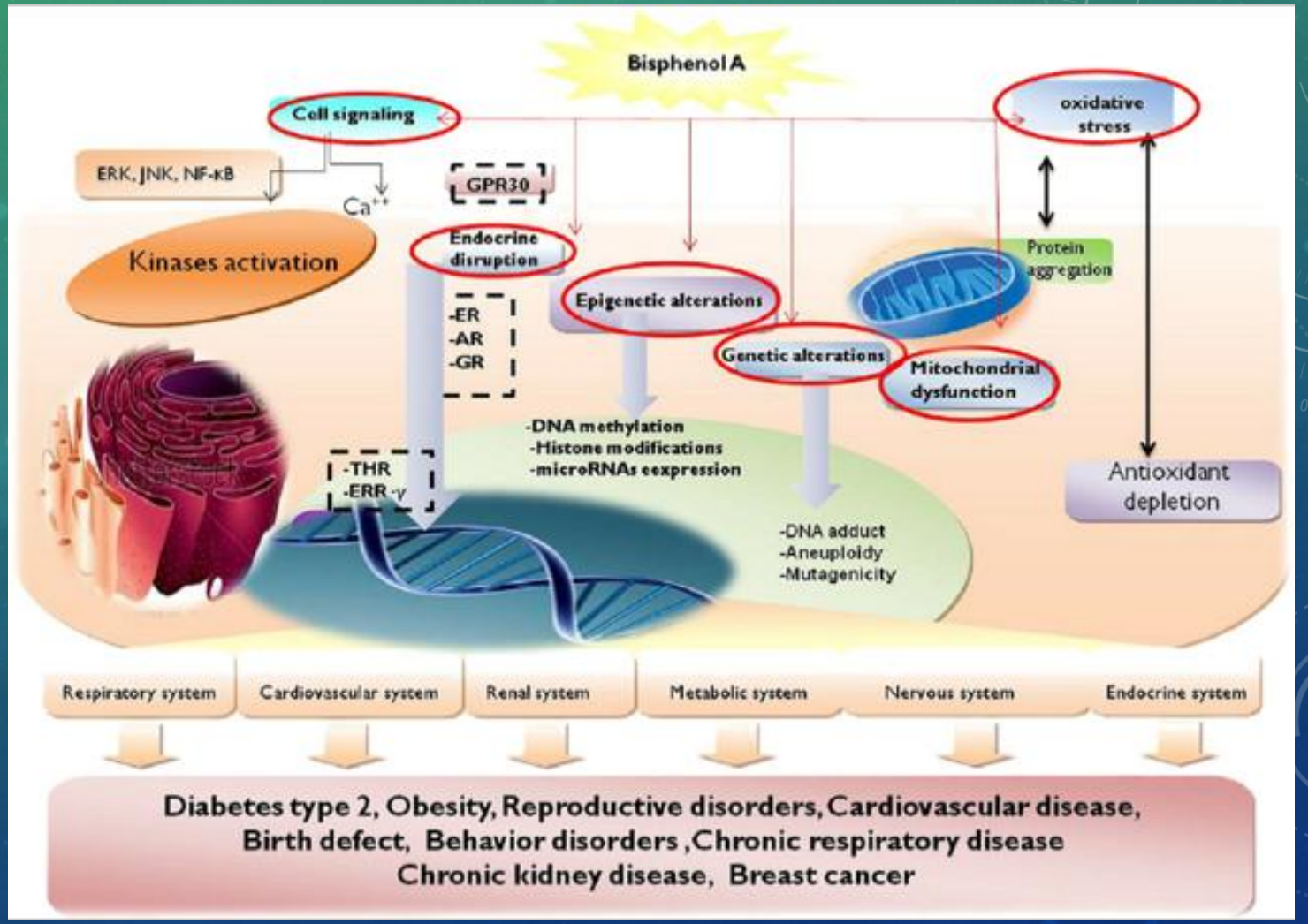

Manmade source of phthalates as plasticizers
Air
Soil
Water
Direct exposure
Animals
Medicinal and food plants
Marines and algae
Liver
Reproductive system
Brain
Kidney

BPA EXPOSU


BPA Exposure
Liver
Pancreas
Muscle
Adipose Tissue
Hypothalamus
↑ Glucose
↓ Glicogen
↓ Insulin receptors and signaling
↑↓ Insulin production and release
↓ Glucose utilization
↓ Insulin sensitivity
↑ Leptin
↓ Adiponectin
↓ Glucose utilization
↑ Fatty acids accumulation
↓ POMC
↑ NPY/AgRP

BPA EXPOSURE

higher levels of urinary bisphenol A (BPA) were associated with an increased risk for obesity in children participating in the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2010.



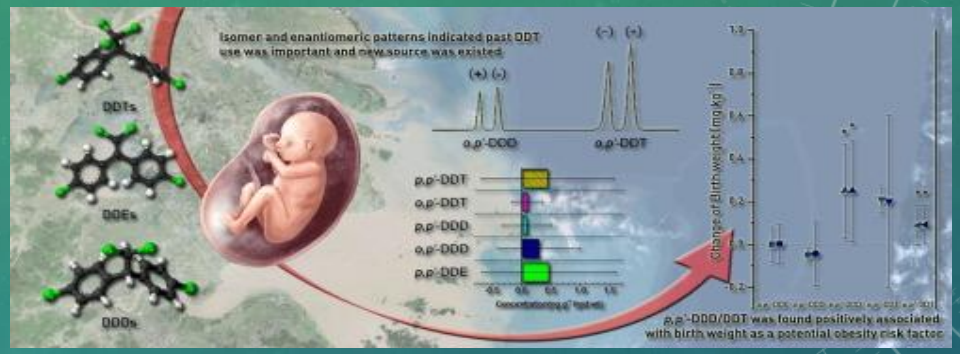
BPA EXPOSURE

BPS may be as efficacious as BPA in changing brain development and behavior

http://wholepregnancy.org/index.php?id=videos_articles&art_topicid=23

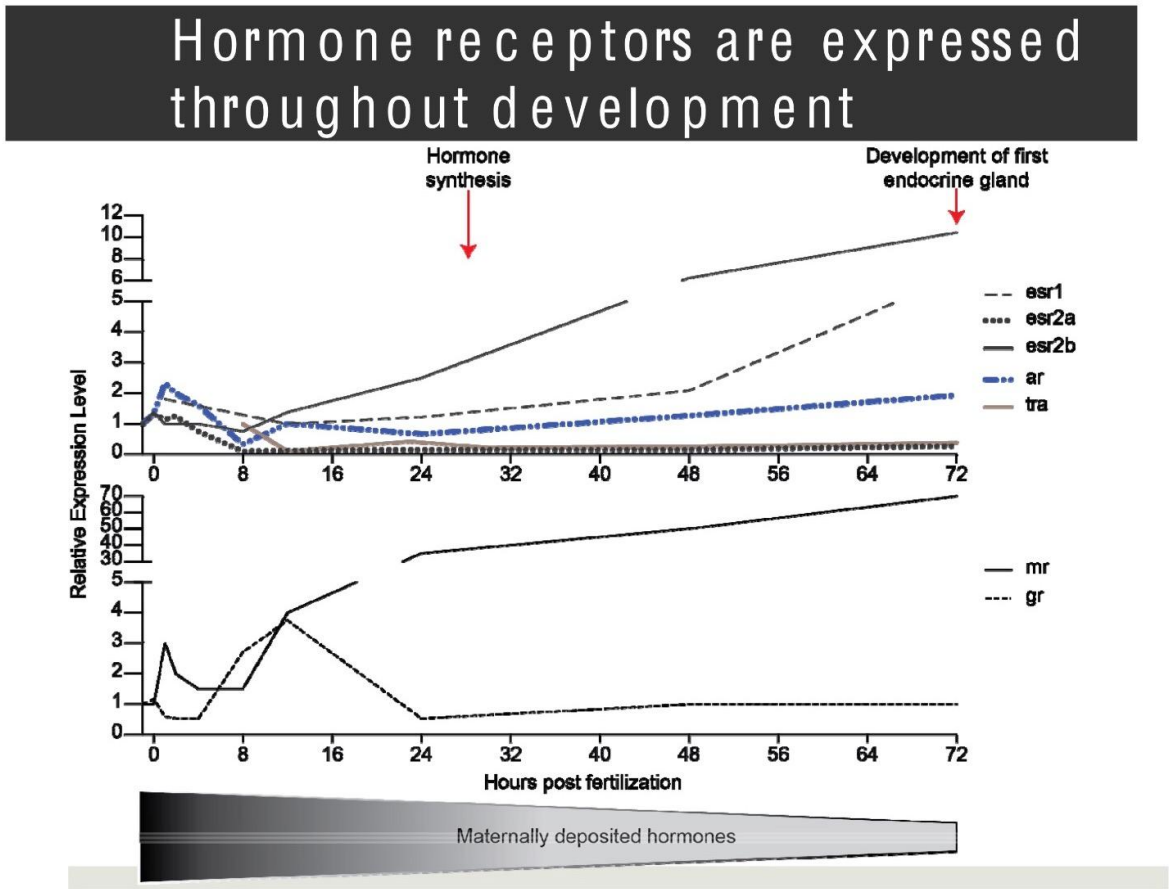
Kinch et al, 2015 *PNAS*


GENDER-BENDING CHEMICALS
PHTHALATES: Found in vinyl flooring, shower curtains, solvents, plastics, PVC. Banned in cosmetics made in EU.
PARABENS: Preservatives used in cosmetics, creams, lotions and deodorants.
TRICLOSAN: Anti-bacterial chemical used in soaps, toothpaste and chopping boards.
PCBs: Found in electrical circuits, paints, brake linings and flame retardants. Banned in EU.
BISPHENOL A: Used in clear plastic baby bottles, tin cans, mobile phone casings. Banned in baby bottles in Canada.
LINURON/DIURON: Herbicides used to control weeds on roads, forests and farms. Traces found on food.
VINCLOZOLIN: Fungicide banned in EU, but found on imported fruit and vegetables.
PENTA-BDE: Flame retardants, now banned in EU, found in old foam mattresses and car seats.
PROCHLORAZ: Fungicide used on fruits and vegetables.
PROCYMIDONE: Fungicide banned in EU last year, traces found in UK beans, fruit smoothies and breakfast cereal.
Source: CHEM TRUST


Isomer and enantiomeric patterns indicated past DDT use was important and new source was existed.
DDTs
DDEs
DDDs
o,p'-DDD
o,p'-DDT
p,p'-DDT
o,p'-DDT
p,p'-DDD
o,p'-DDD
p,p'-DDE
p,p'-DDD/DDT was found positively associated with birth weight as a potential obesity risk factor.

EDC EARLY EXPOSURE IN LIFE

Pesticide DDT linked to slow Metabolism, Obesity, Diabetes, Cholesterol and affected Offspring



ARE THEY REALLY **BPA FREE**?

What about BPA-free products?

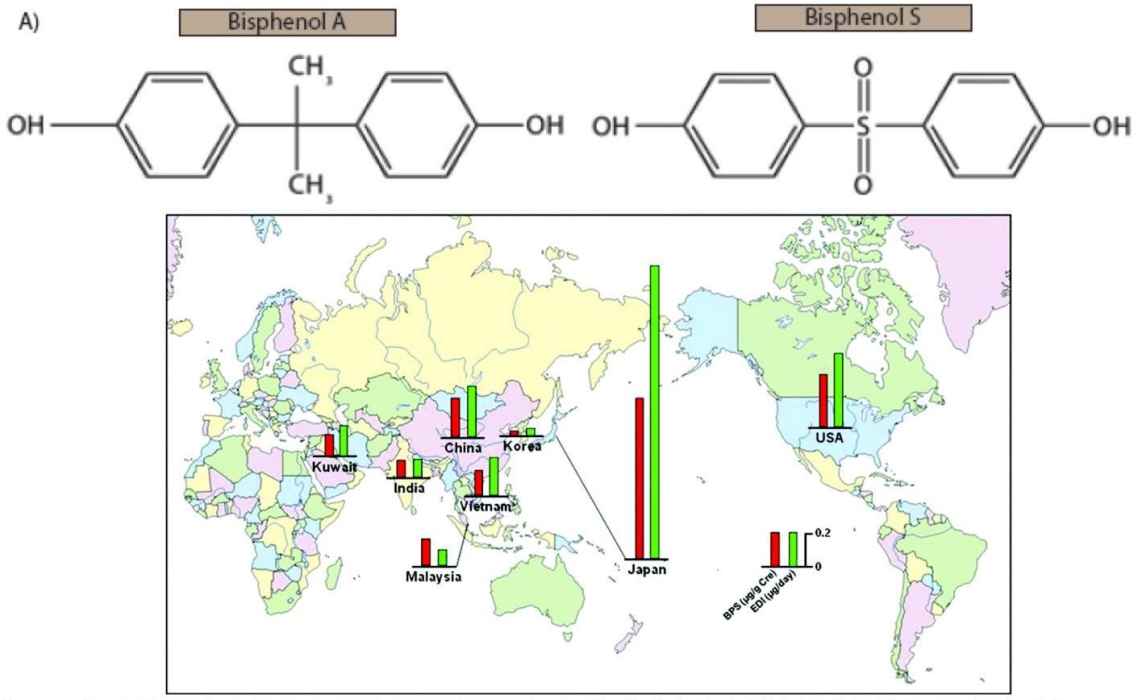
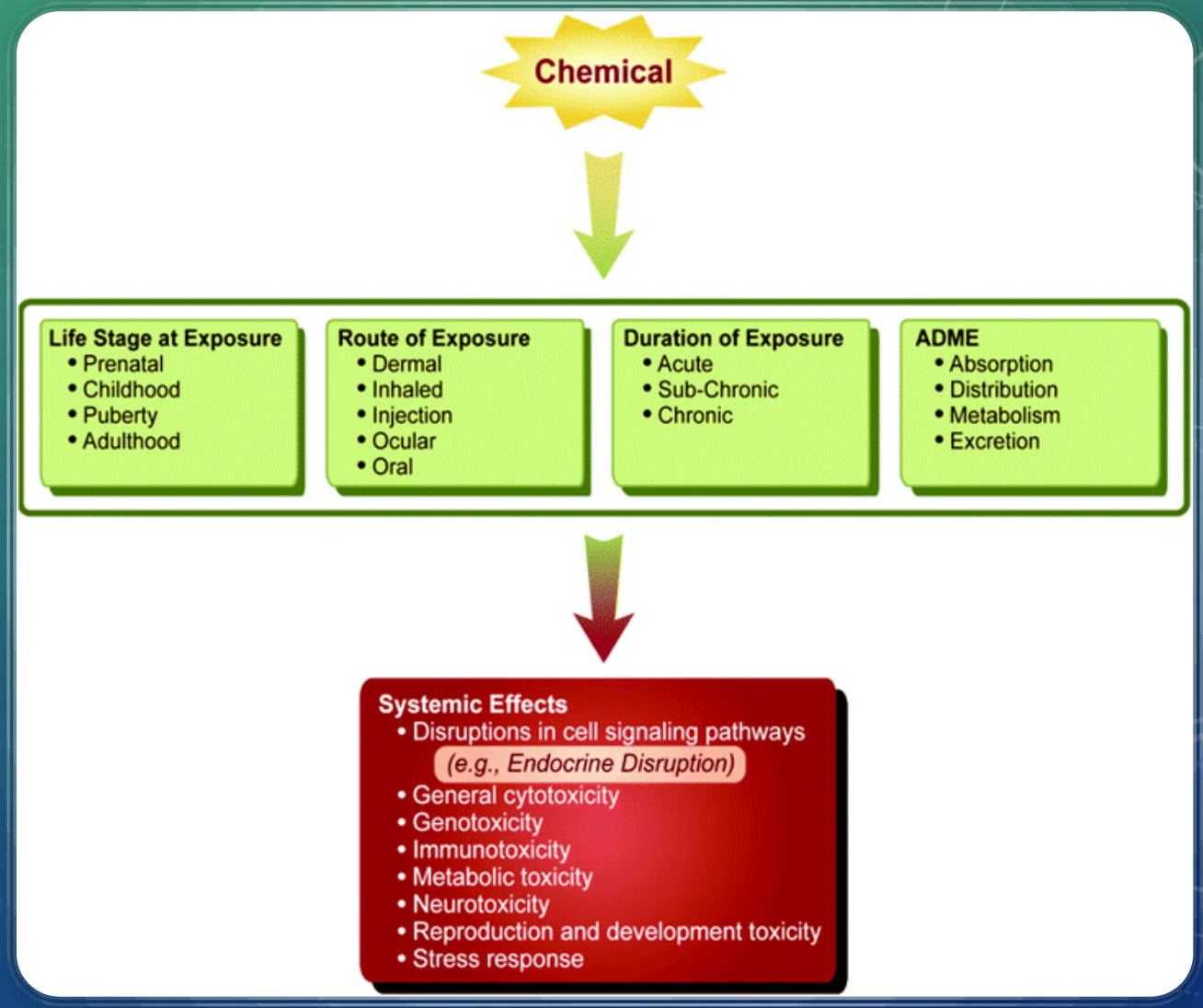
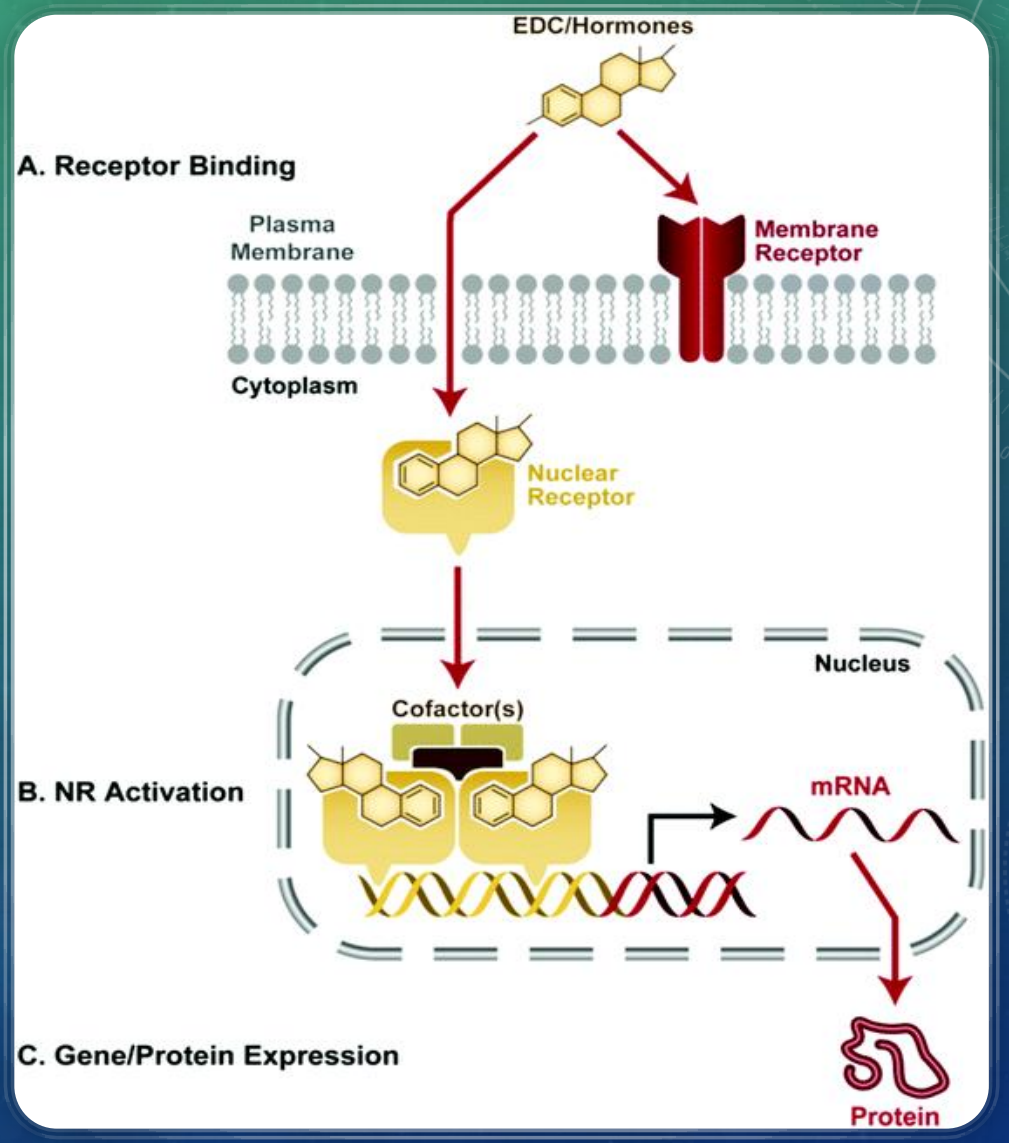


Image courtesy of: http://firstdescents.org/wp-content/uploads/2012/03/bpa-free.jpg; Liao, C., Liu, F., Alomirah, H., Loi, V., Mohd, M., Moon, H., Nakata, H., Kannan, K. 2012 Bisphenol S in urine from United States and seven Asian countries: Occurrence and human exposures. Environmental Science & Technology 46: 6860-6866

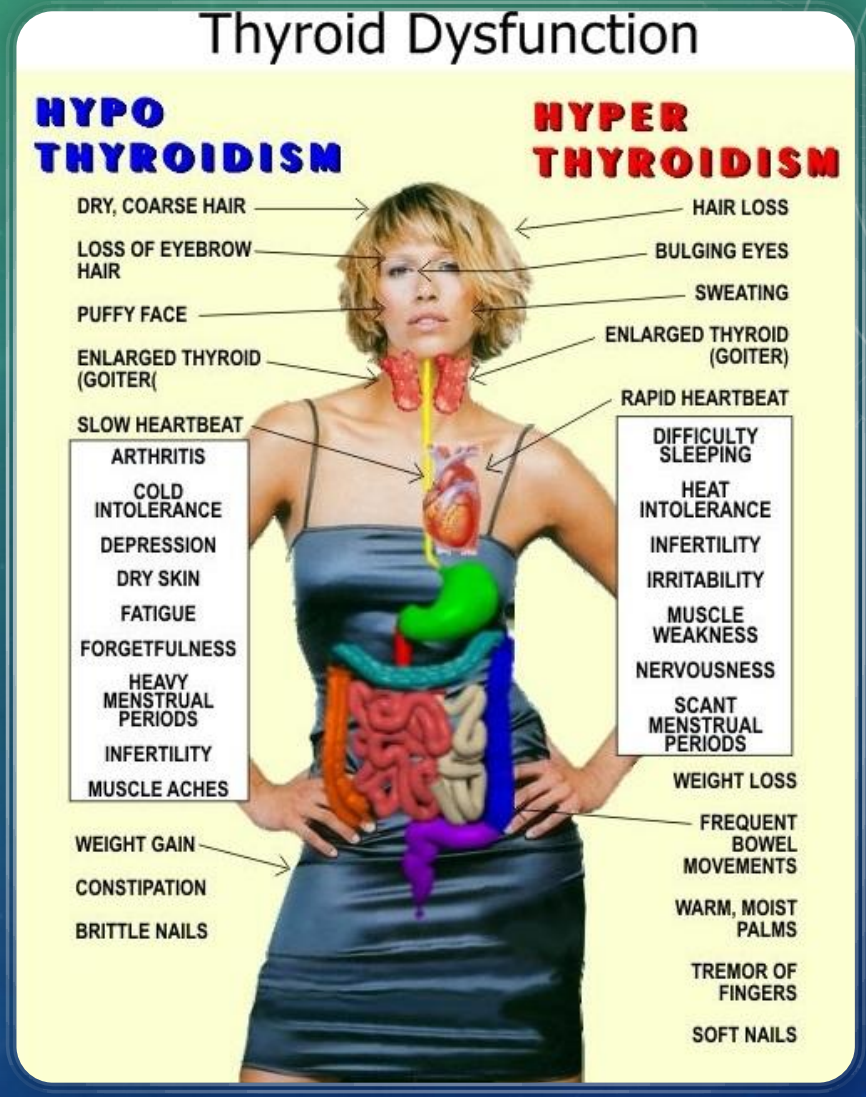
MECHANISM OF ACTION



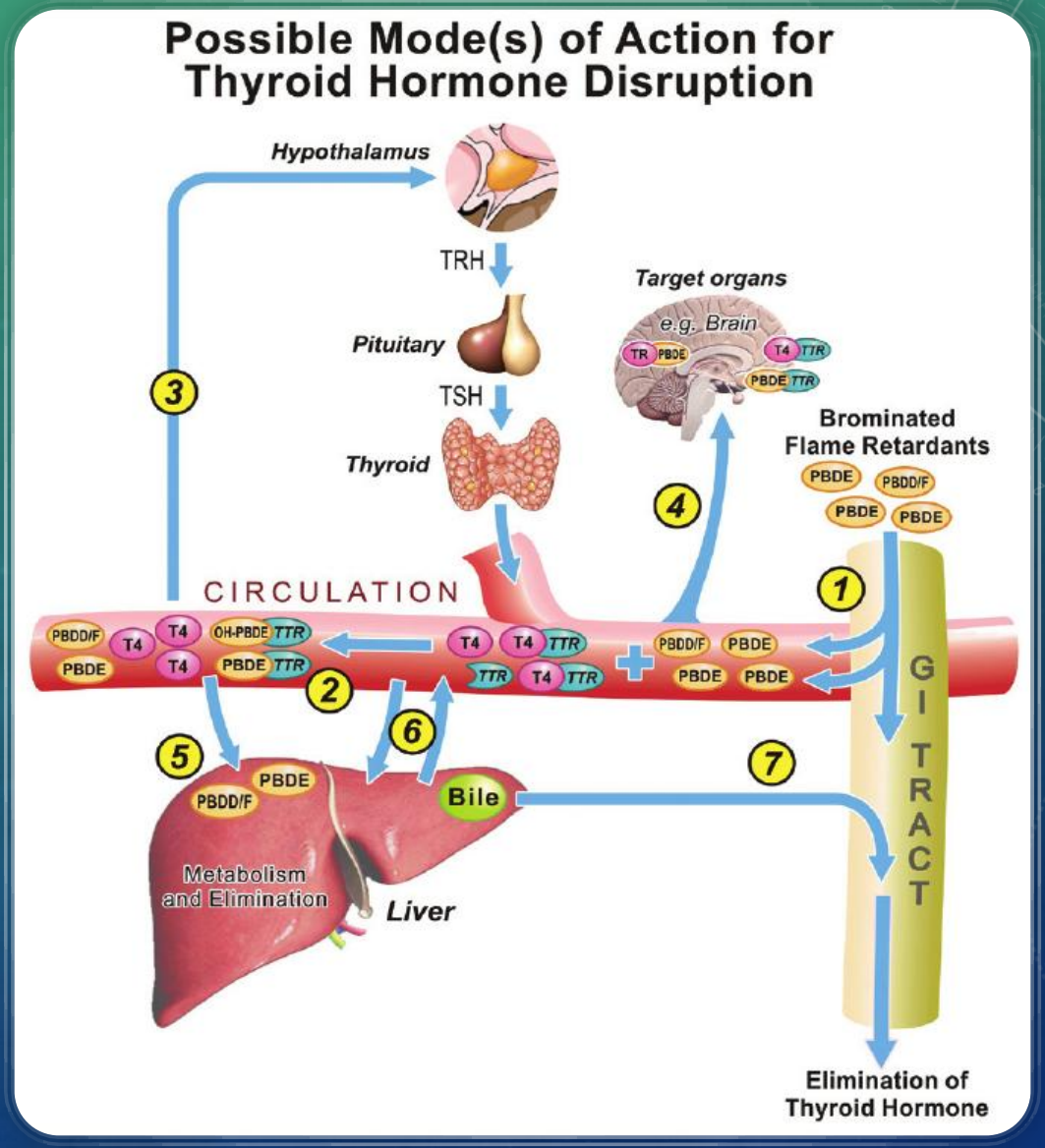
EDC AND GENES



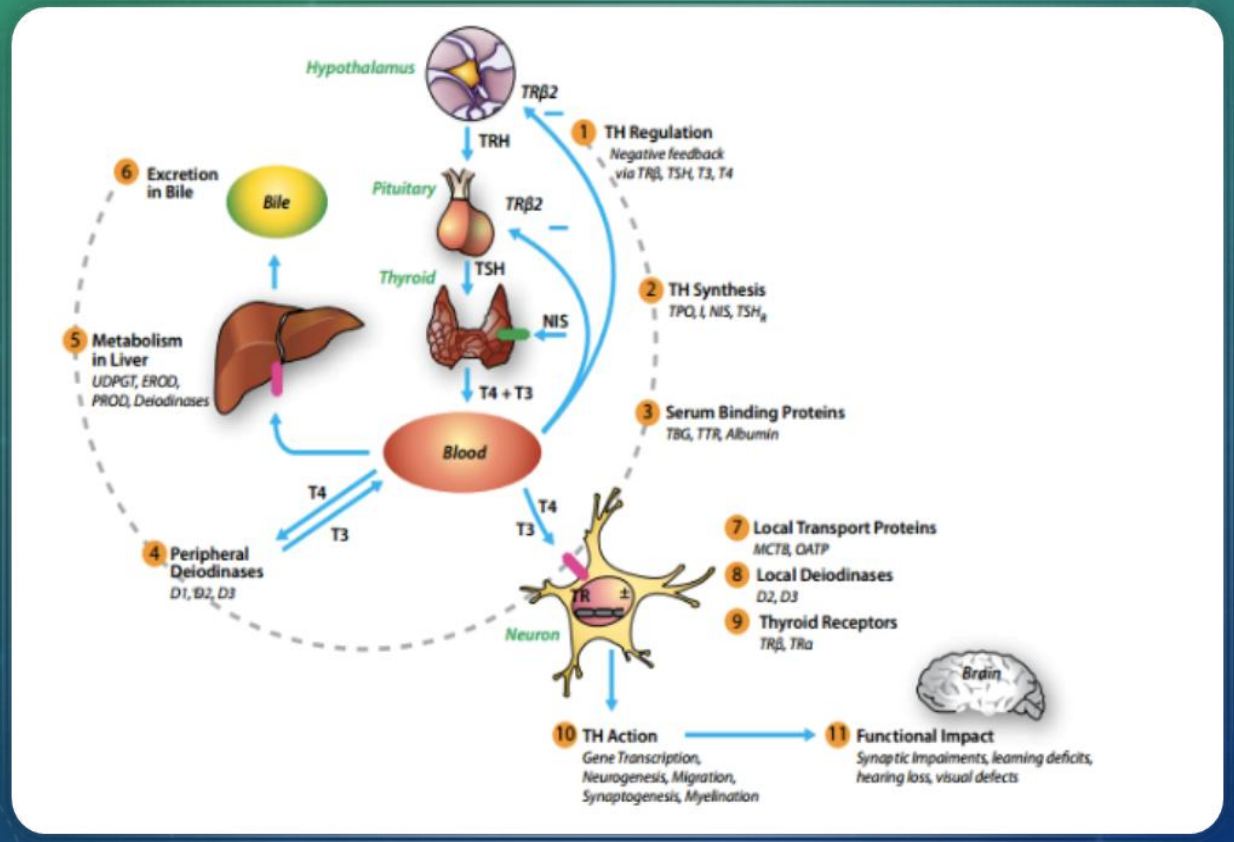
THYROID DISORDER

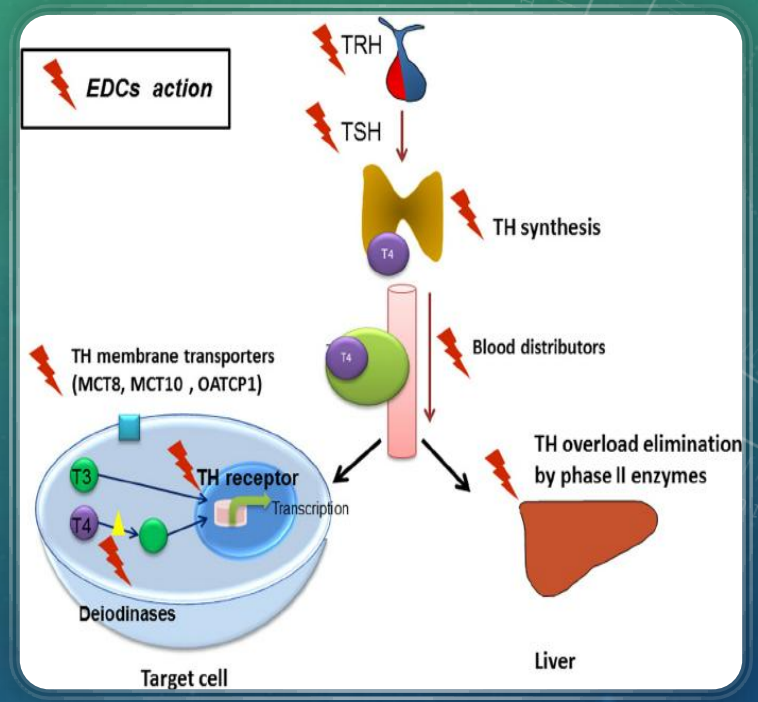


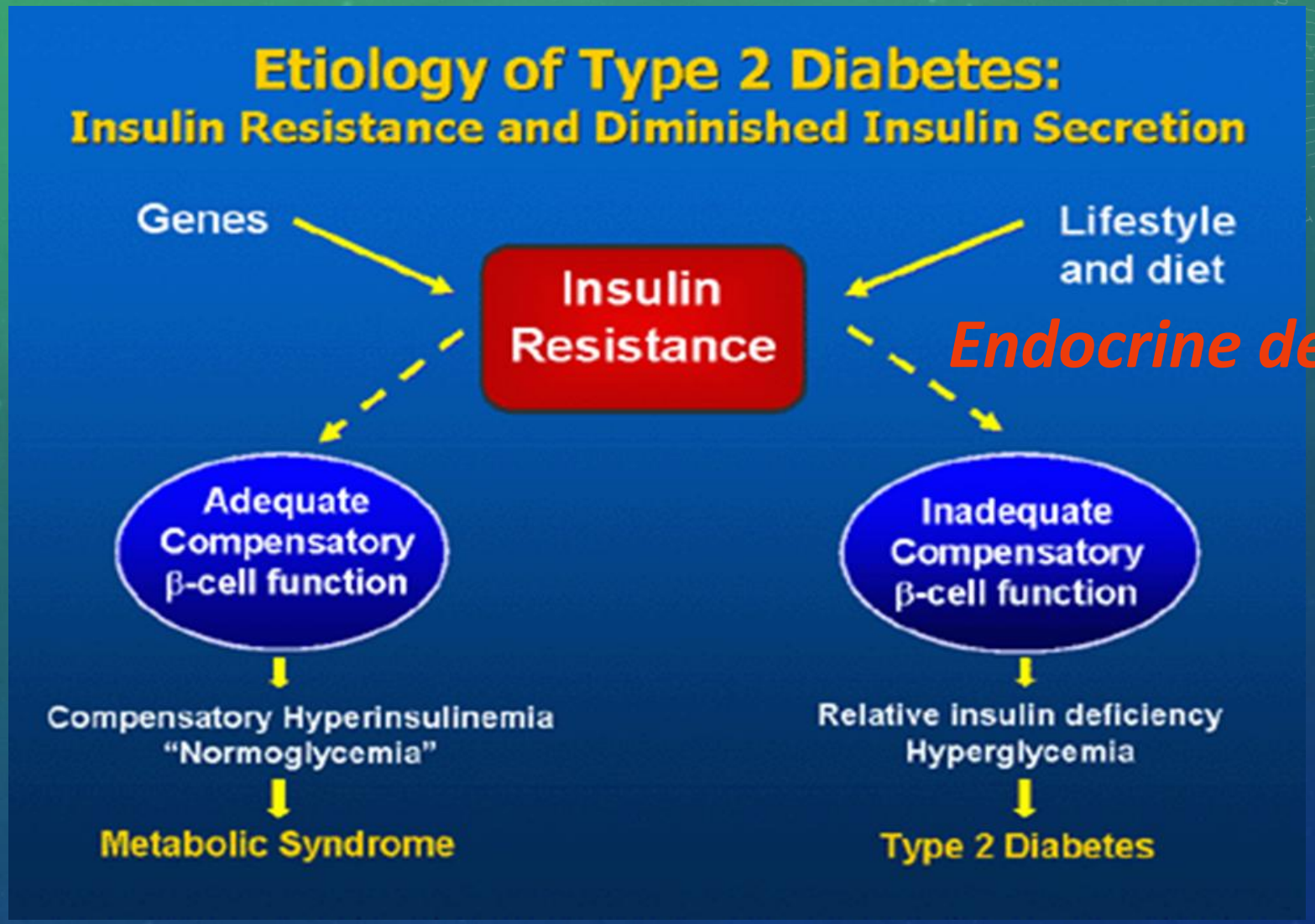
EDC EFFECTS ON THYROID

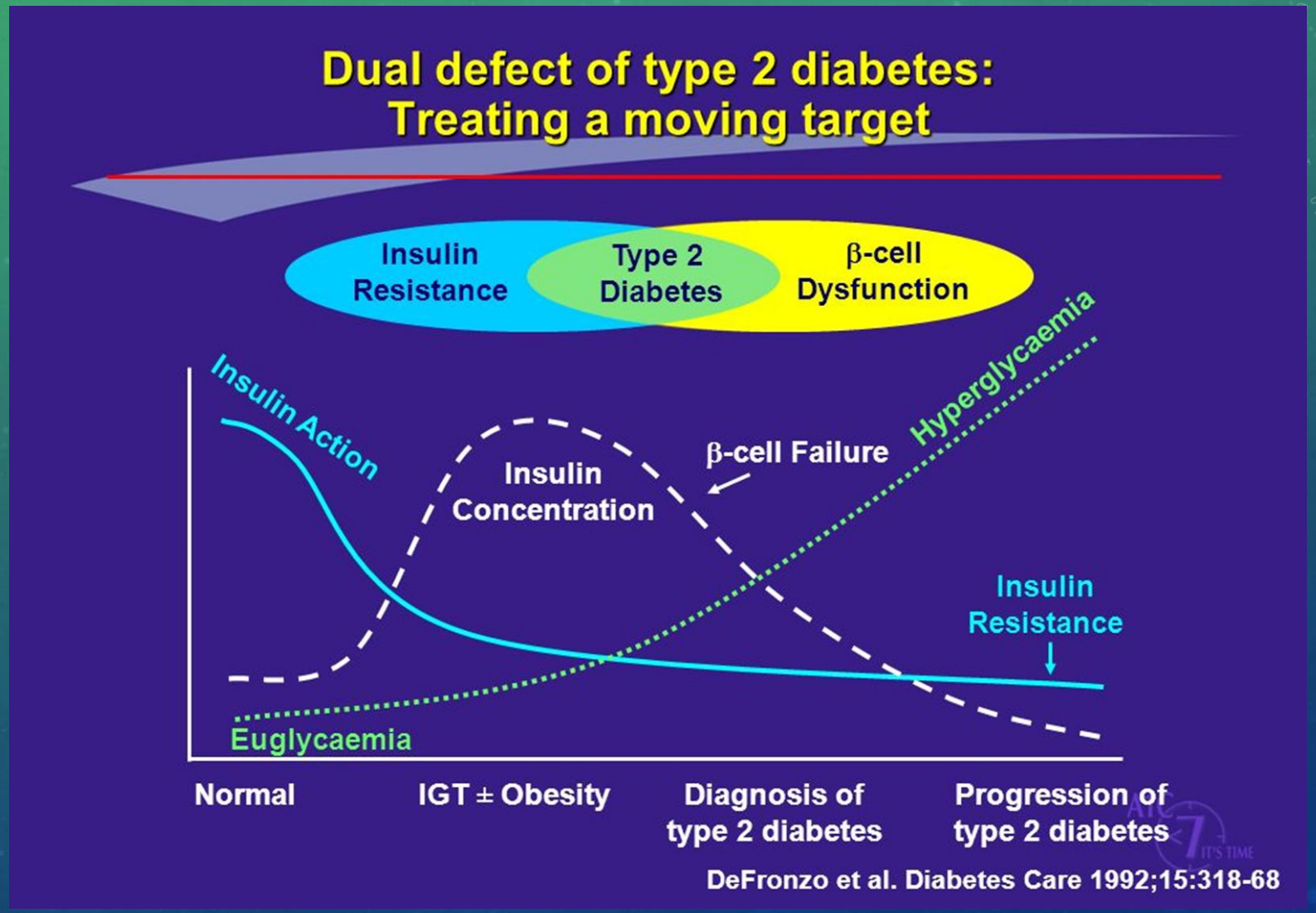


EDC EFFECTS ON THYROID

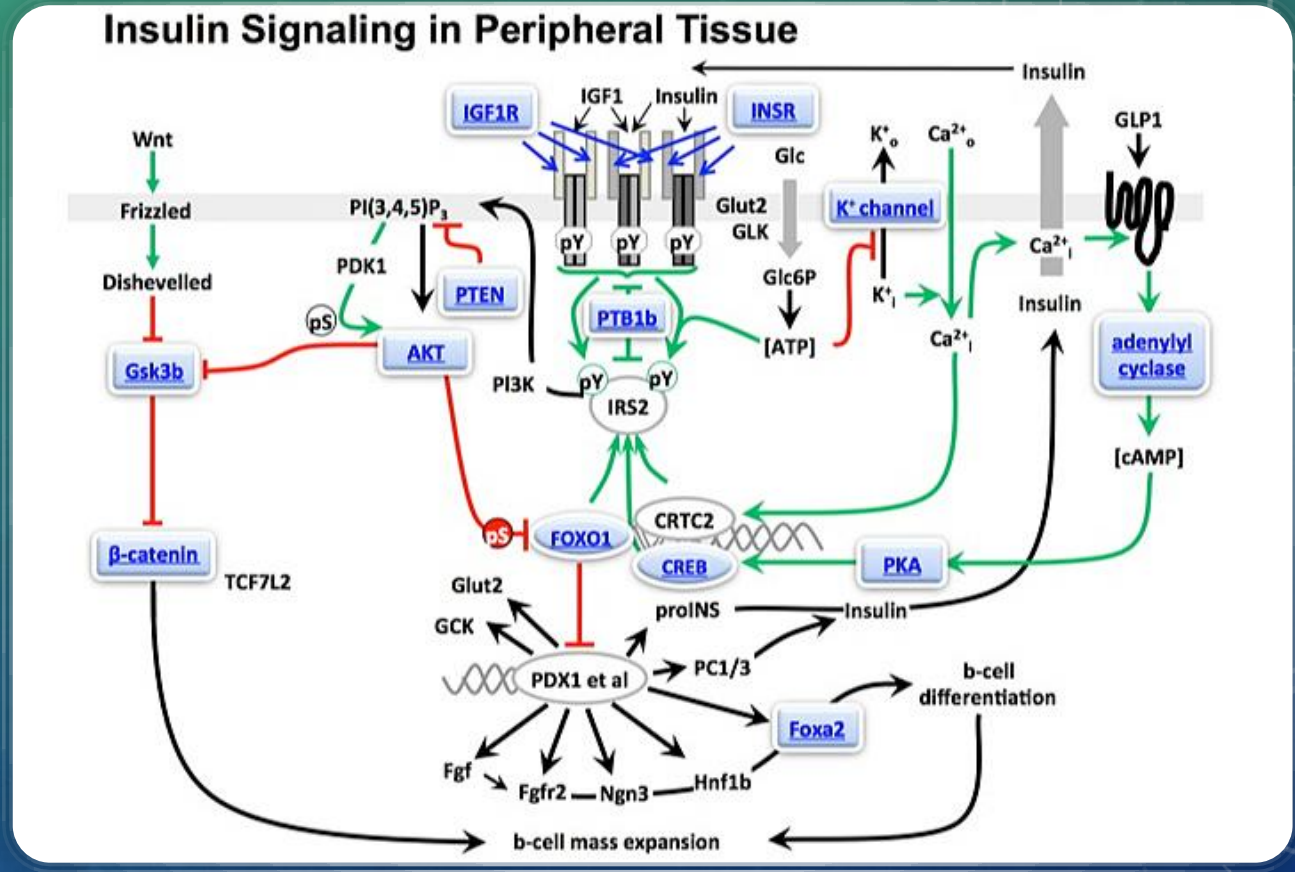


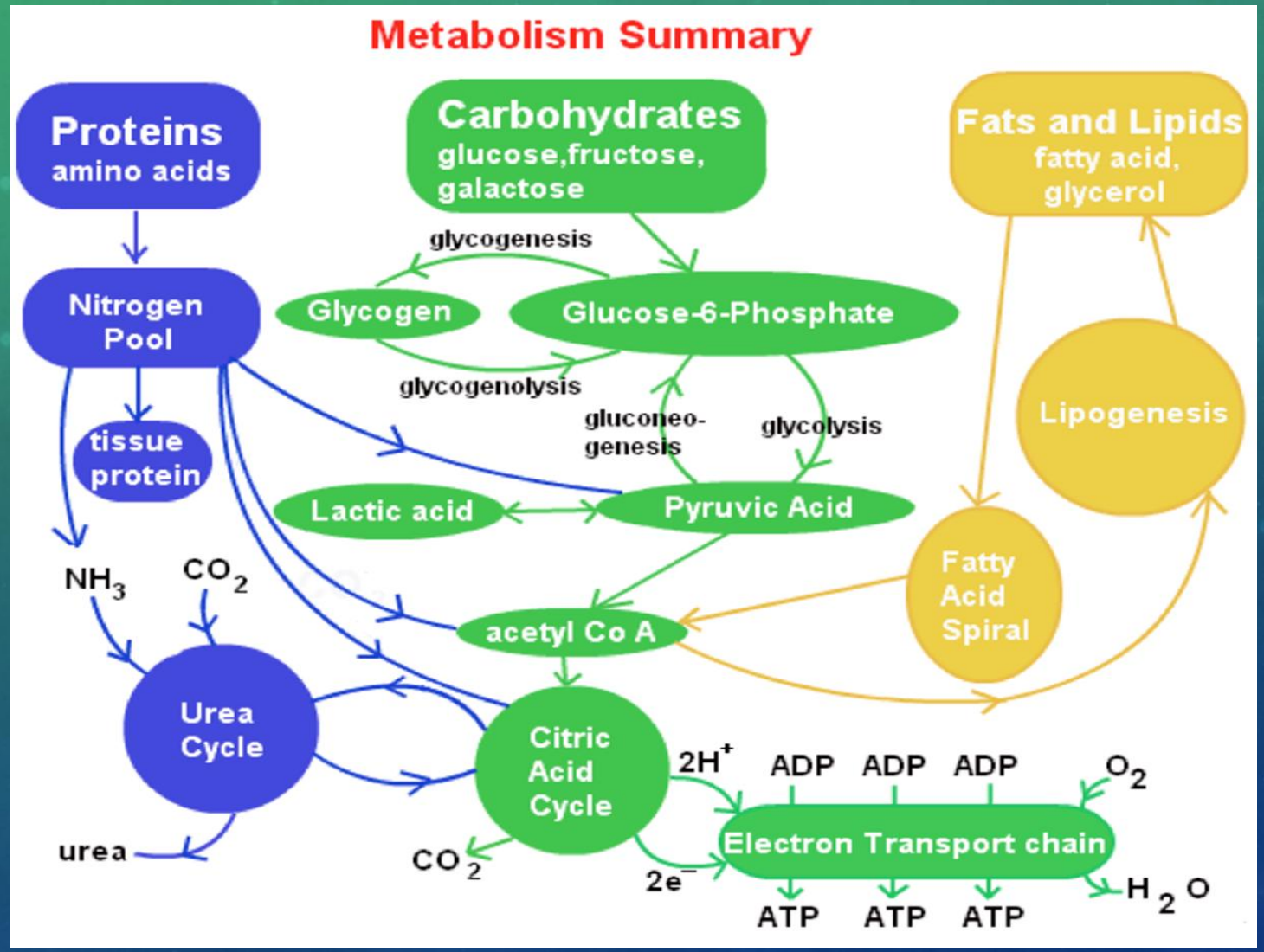



Etiology of Type 2 Diabetes:
Insulin Resistance and Diminished Insulin Secretion
Genes
Lifestyle and diet
Insulin Resistance
Endocrine destructor
Adequate Compensatory β-cell function
Inadequate Compensatory β-cell function
Compensatory Hyperinsulinemia "Normoglycemia"
Relative insulin deficiency Hyperglycemia
Metabolic Syndrome
Type 2 Diabetes


Dual defect of type 2 diabetes:
Treating a moving target
Insulin Resistance
Type 2 Diabetes
β-cell Dysfunction
Insulin Action
Insulin Concentration
β-cell Failure
Hyperglycaemia
Insulin Resistance
Euglycaemia
Normal
IGT ± Obesity
Diagnosis of type 2 diabetes
Progression of type 2 diabetes
DeFronzo et al. Diabetes Care 1992;15:318-68

EDC EFFECTS ON INSULIN SIGNALING




Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose,fructose,
galactose
Fats and Lipids
fatty acid,
glycerol
glycogenesis
Nitrogen
Pool
Glycogen
Glucose-6-Phosphate
glycogenolysis
gluconeo-
genesis
glycolysis
Lipogenesis
tissue
protein
Lactic acid
Pyruvic Acid
NH3
CO2
Fatty
Acid
Spiral
acetyl Co A
Urea
Cycle
Citric
Acid
Cycle
2H+
ADP
ADP
ADP
O2
Electron Transport chain
urea
CO2
2e−
H2O
ATP
ATP
ATP

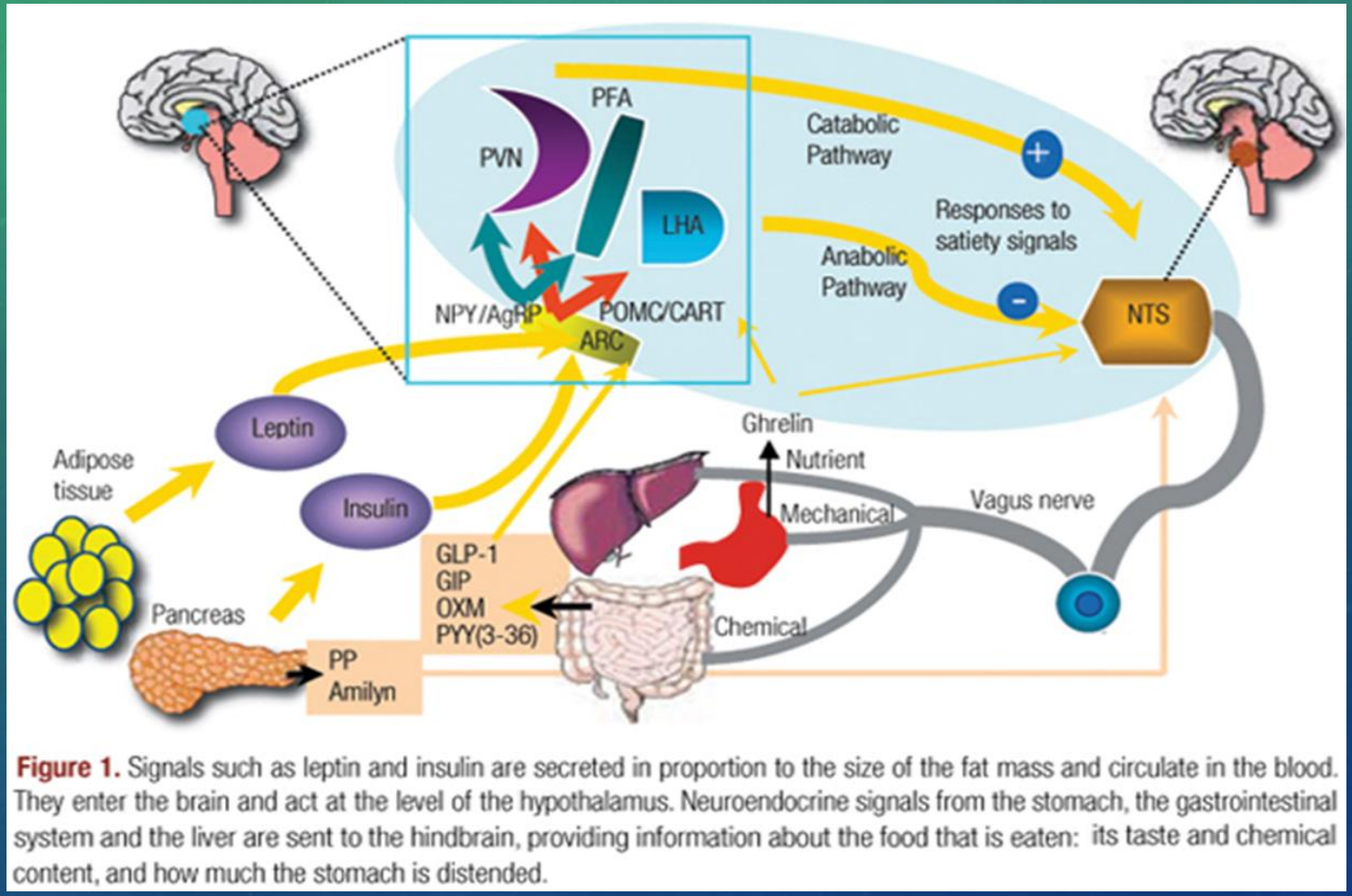
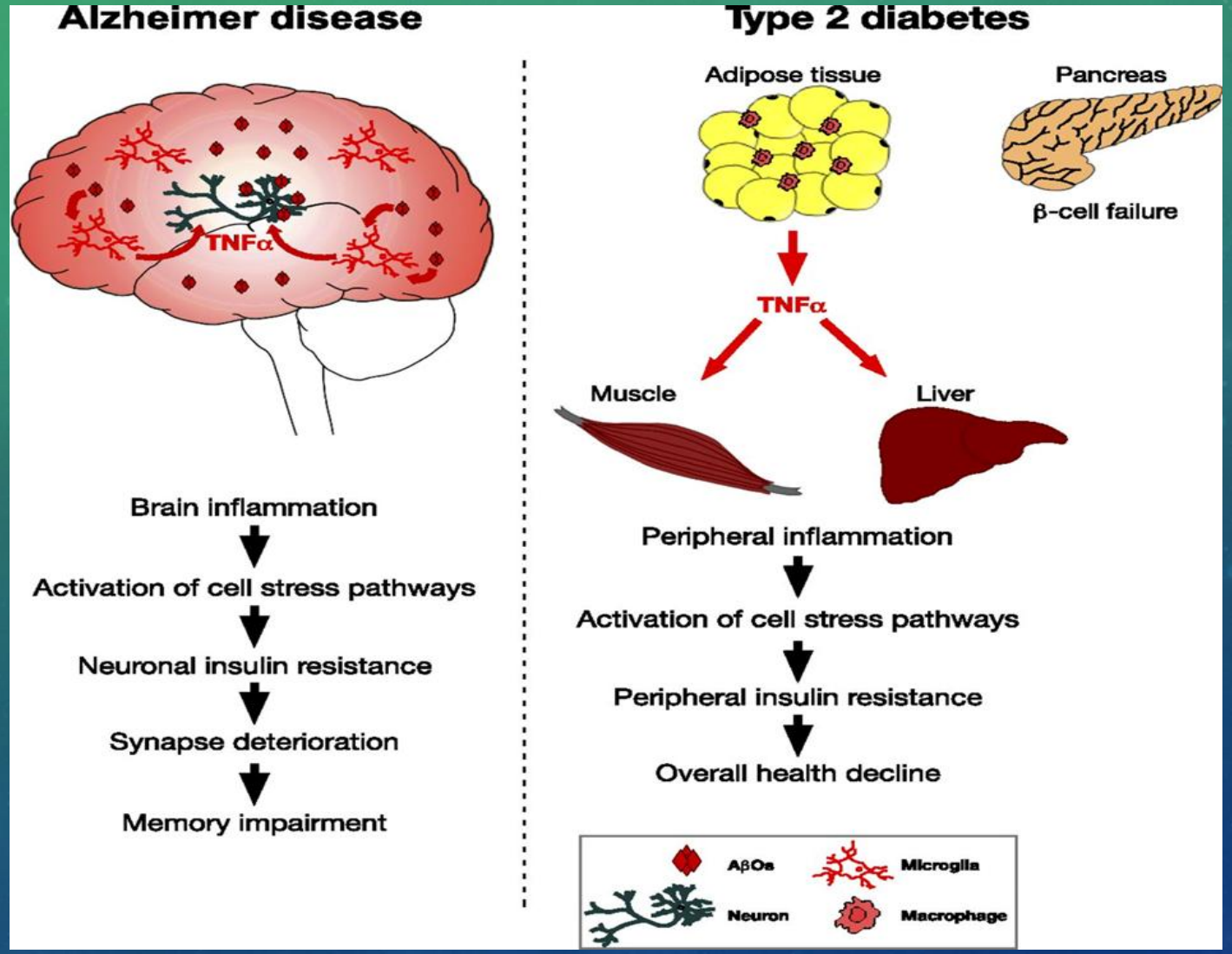
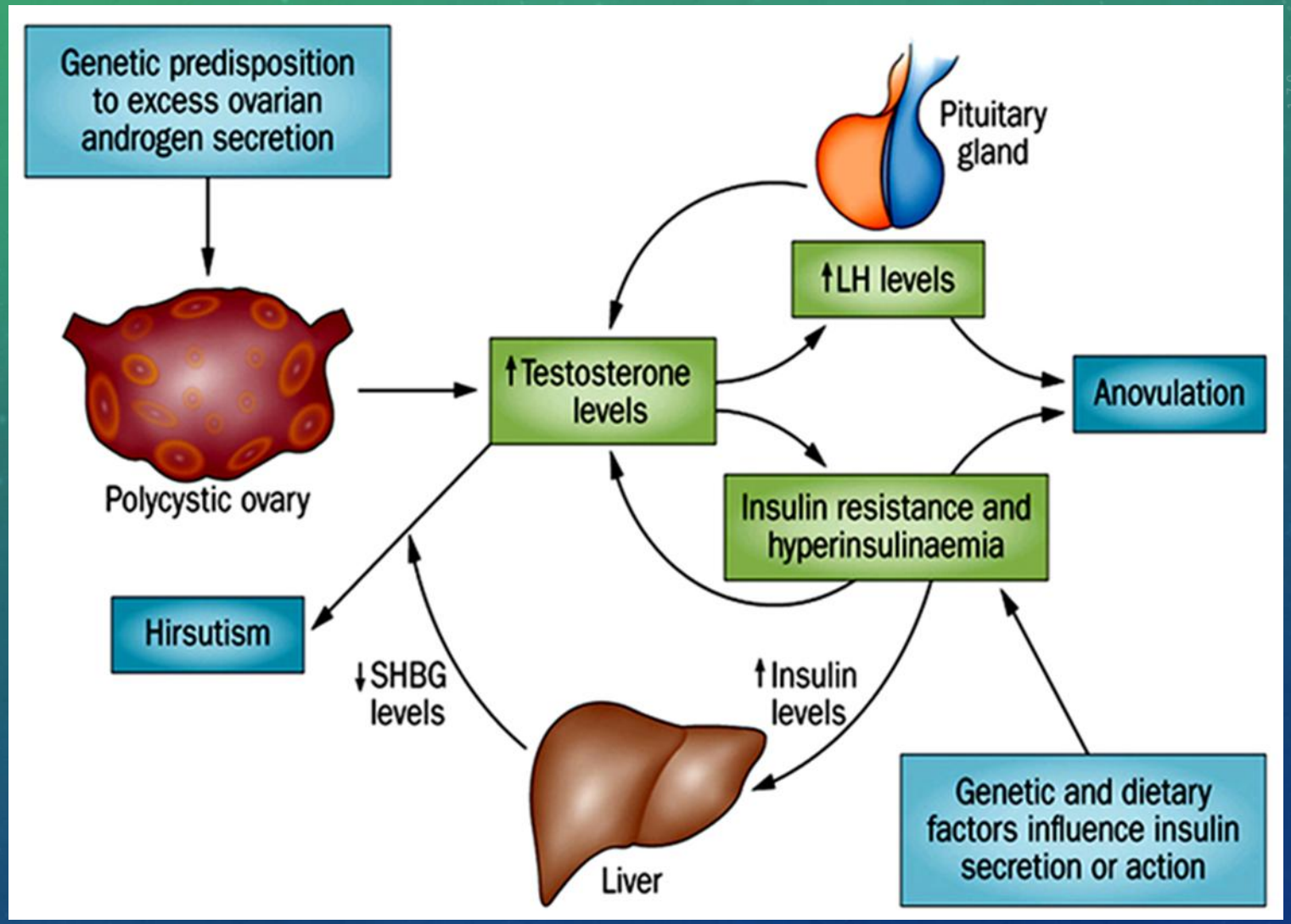
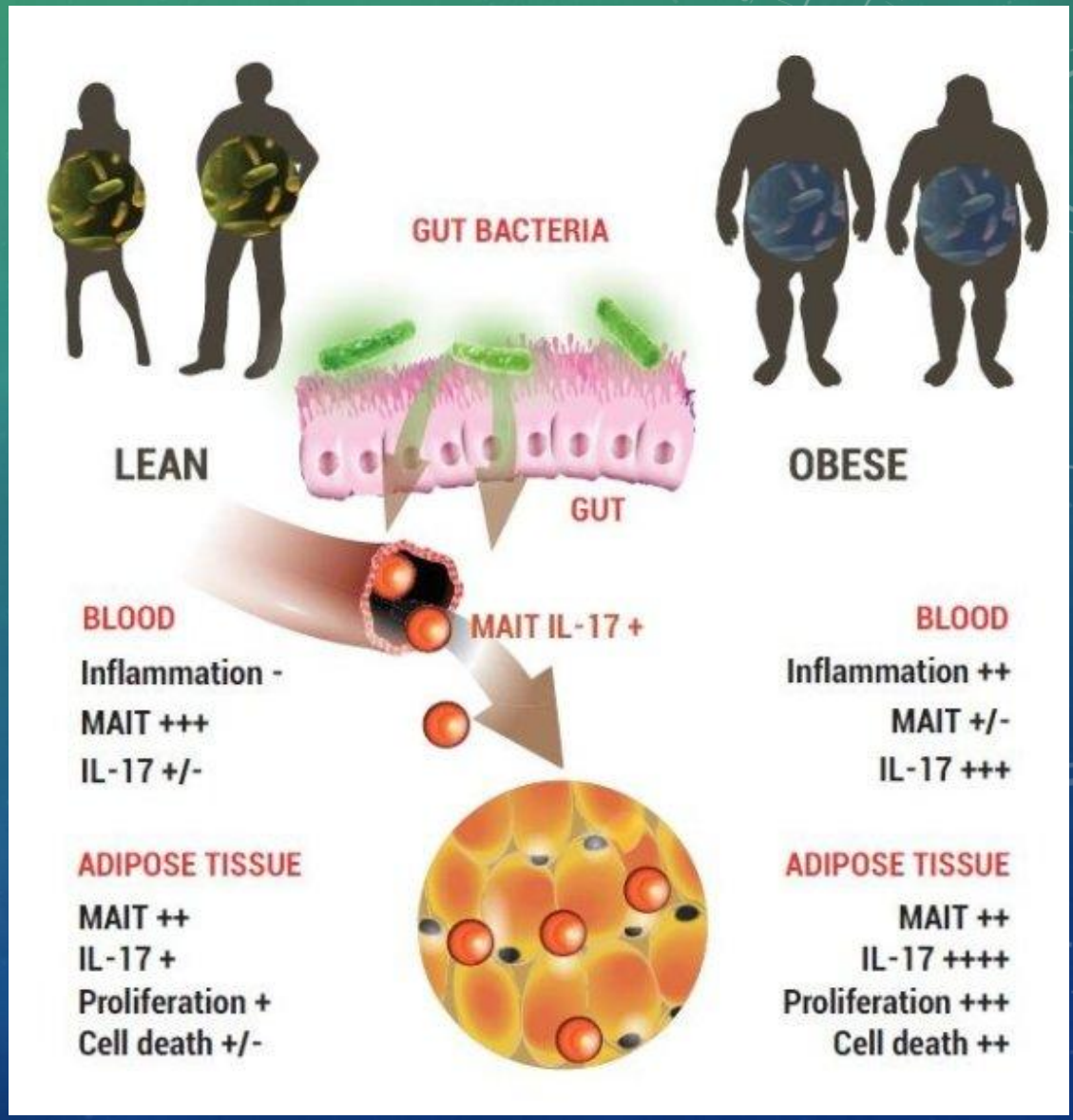


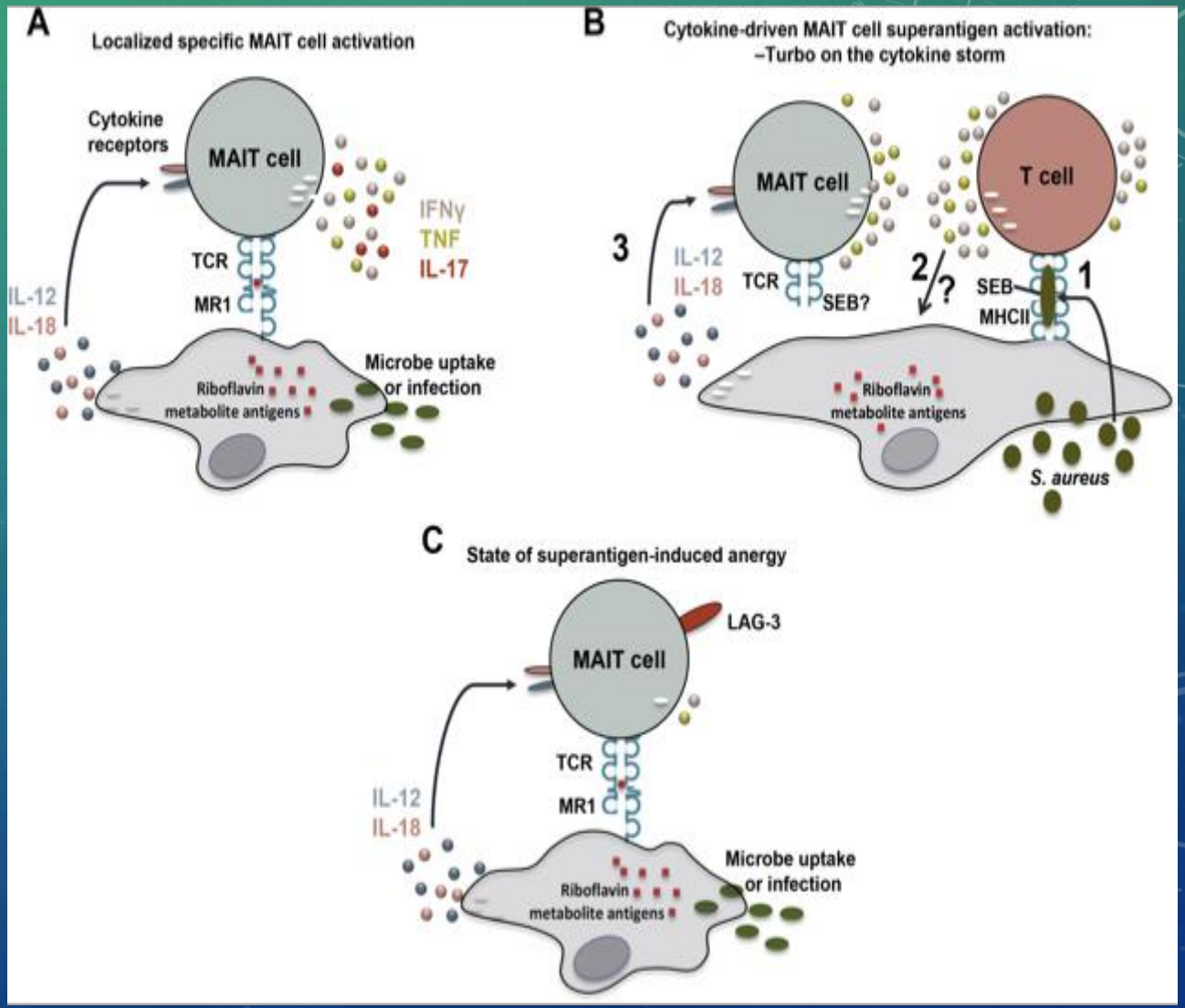
Figure 1. Signals such as leptin and insulin are secreted in proportion to the size of the fat mass and circulate in the blood. They enter the brain and act at the level of the hypothalamus. Neuroendocrine signals from the stomach, the gastrointestinal system and the liver are sent to the hindbrain, providing information about the food that is eaten: its taste and chemical content, and how much the stomach is distended.


Alzheimer disease
TNFα
Brain inflammation
Activation of cell stress pathways
Neuronal insulin resistance
Synapse deterioration
Memory impairment
Type 2 diabetes
Adipose tissue
Pancreas
β-cell failure
TNFα
Muscle
Liver
Peripheral inflammation
Activation of cell stress pathways
Peripheral insulin resistance
Overall health decline
AβOs
Microglia
Neuron
Macrophage

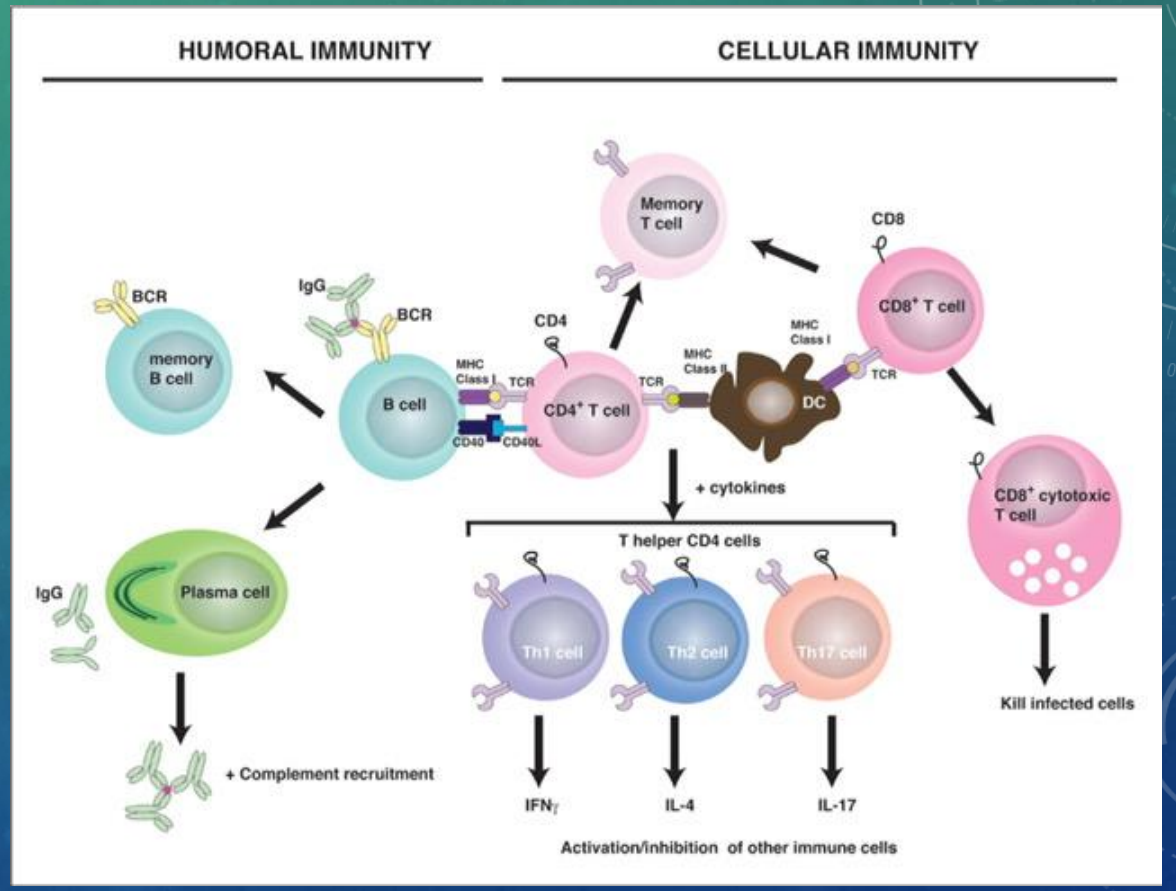

Genetic predisposition to excess ovarian androgen secretion
Pituitary gland
↑LH levels
Polycystic ovary
↑Testosterone levels
Anovulation
Insulin resistance and hyperinsulinaemia
Hirsutism
↓SHBG levels
↑Insulin levels
Liver
Genetic and dietary factors influence insulin secretion or action

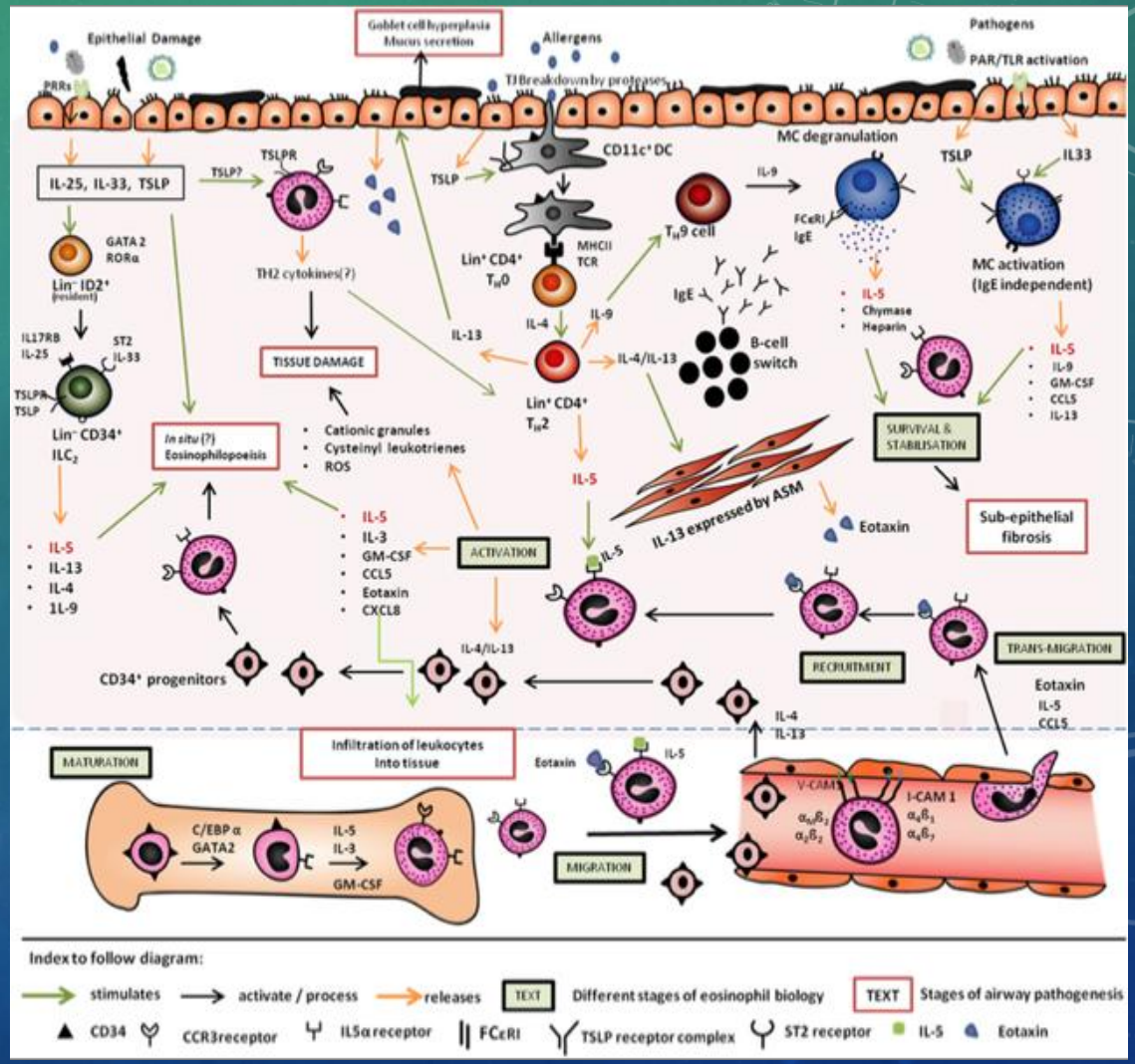
GUT MICROBIOME AND OBESITY

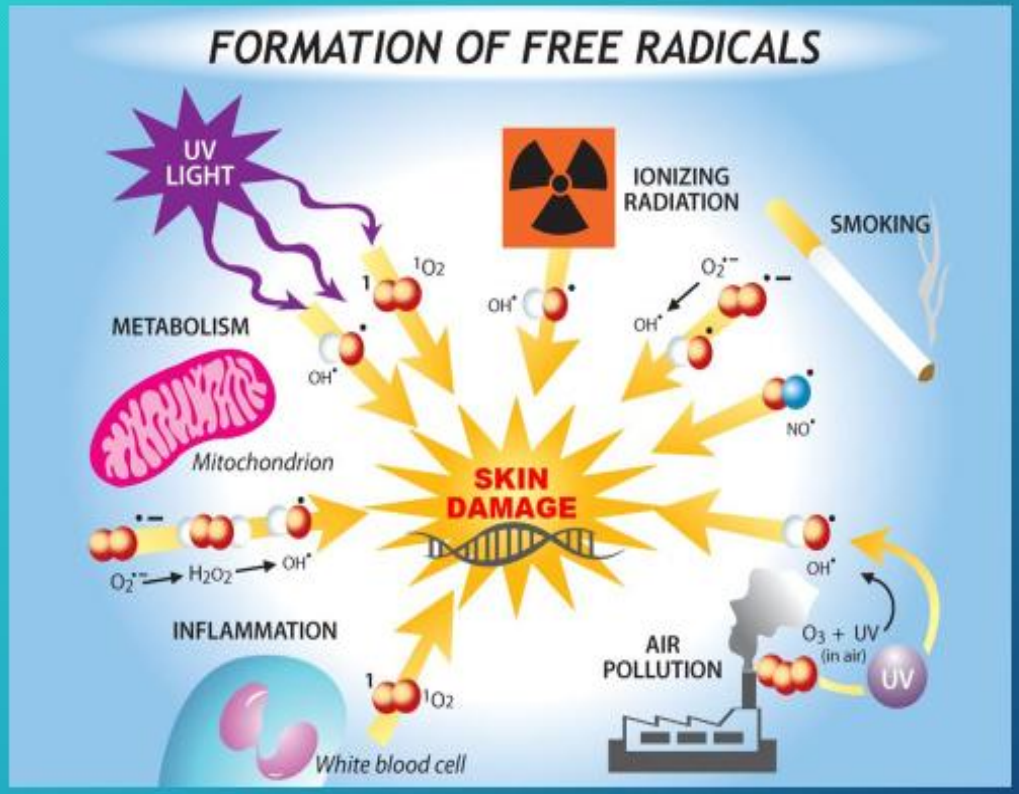


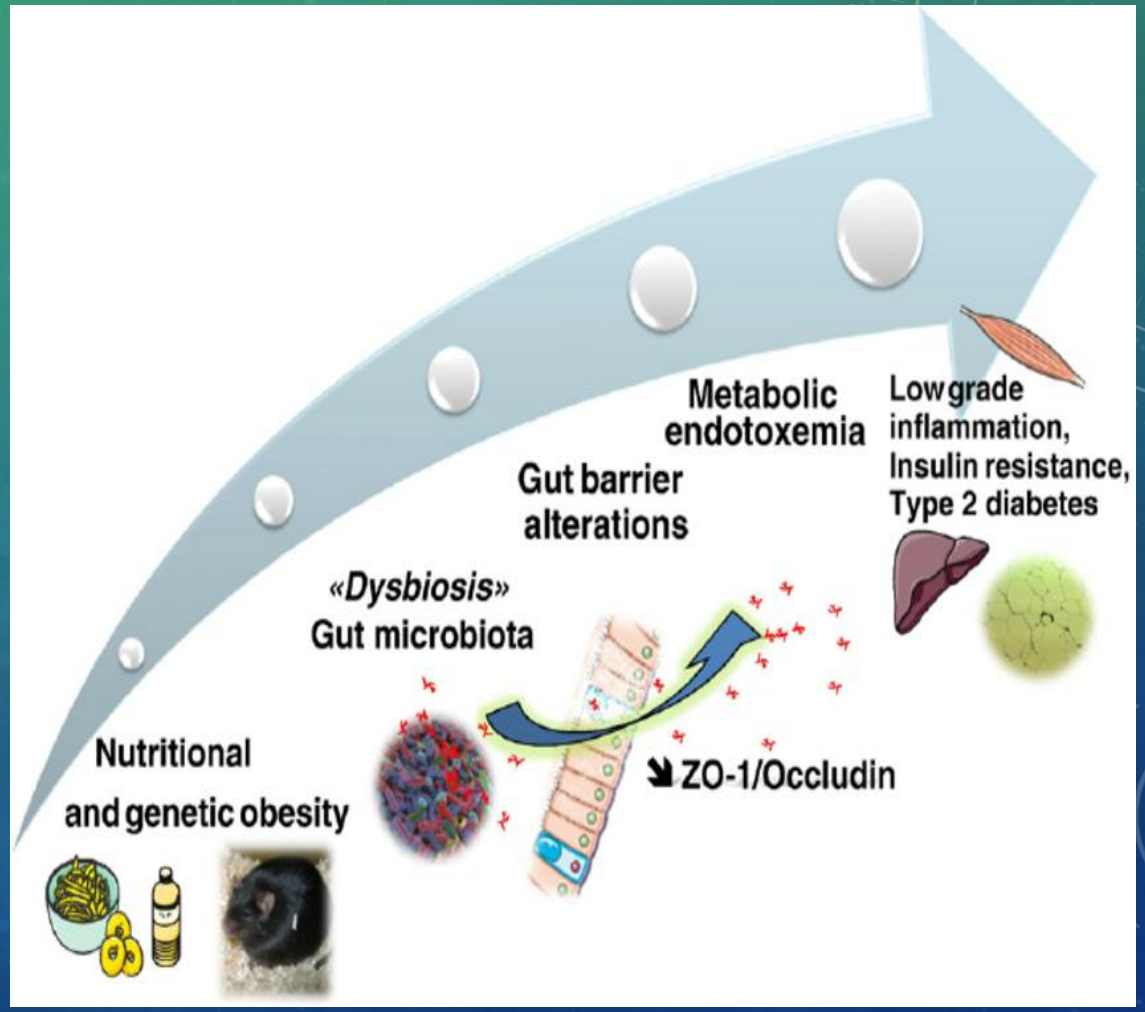

A
Localized specific MAIT cell activation
Cytokine receptors
MAIT cell
IFNγ
TNF
IL-17
TCR
MR1
IL-12
IL-18
Riboflavin metabolite antigens
Microbe uptake or infection
B
Cytokine-driven MAIT cell superantigen activation:
–Turbo on the cytokine storm
MAIT cell
T cell
3
IL-12
IL-18
TCR
SEB?
2/?
SEB
MHCII
1
Riboflavin metabolite antigens
S. aureus
C
State of superantigen-induced anergy
LAG-3
MAIT cell
TCR
MR1
IL-12
IL-18
Riboflavin metabolite antigens
Microbe uptake or infection

IL 17

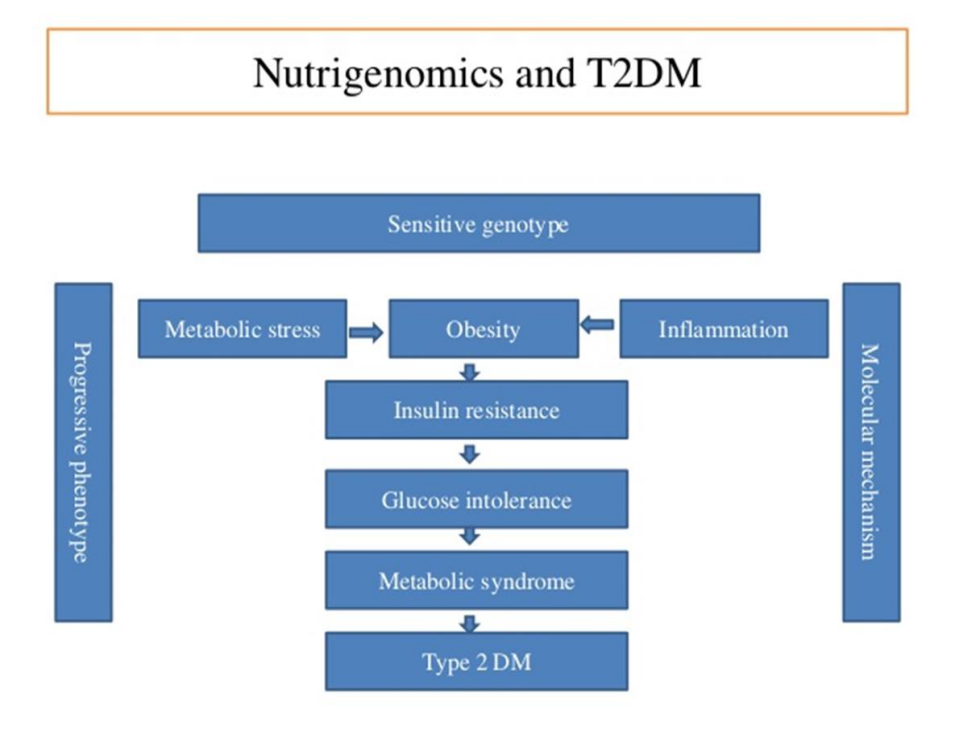

HUMORAL IMMUNITY
CELLULAR IMMUNITY
Memory T cell
CD8
CD8+ T cell
BCR
IgG
BCR
memory B cell
B cell
CD4
MHC Class I
TCR
CD4+ T cell
TCR
MHC Class II
DC
MHC Class I
TCR
CD40
CD40L
+ cytokines
CD8+ cytotoxic T cell
T helper CD4 cells
IgG
Plasma cell
Th1 cell
Th2 cell
Th17 cell
Kill infected cells
+ Complement recruitment
IFNγ
IL-4
IL-17
Activation/inhibition of other immune cells

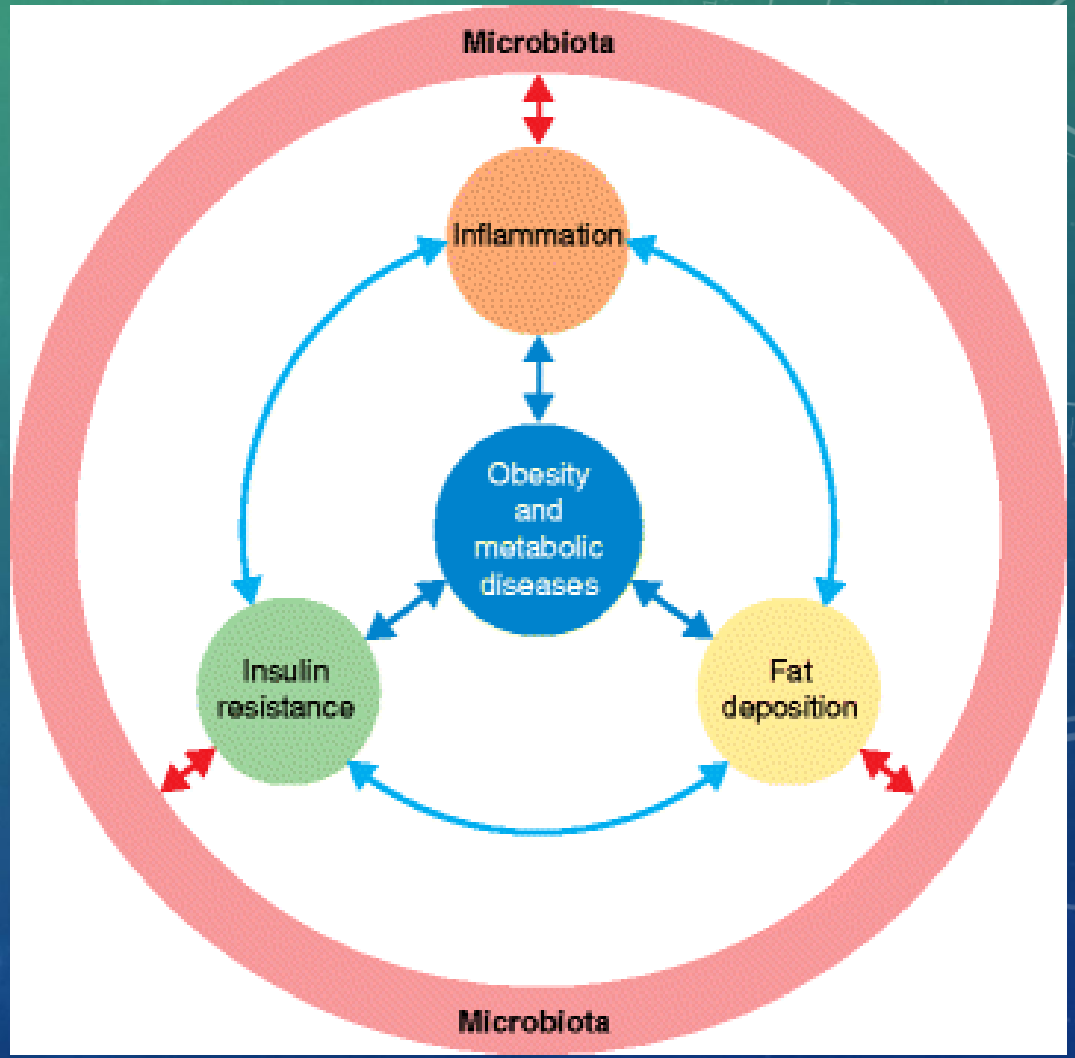

Epithelial Damage
PRRs
Goblet cell hyperplasia
Mucus secretion
Allergens
TJ Breakdown by proteases
Pathogens
PAR/TLR activation
MC degranulation
CD11c⁺ DC
IL-25, IL-33, TSLP
TSLP?
TSLPR
TSLP
IL33
GATA 2
RORα
Lin⁻ ID2⁺
TH2 cytokines(?)
MHCII
TCR
Lin⁺ CD4⁺
T_H0
T_H9 cell
IL-9
FCεRI
IgE
MC activation
(IgE independent)
IL17RB
IL-25
ST2
IL-33
TSLPR
TSLP
Lin⁻ CD34⁺
ILC2
TISSUE DAMAGE
IL-13
IL-4
IL-9
IL-4/IL-13
IgE
B-cell
switch
IL-5
Chymase
Heparin
IL-5
IL-9
GM-CSF
CCL5
IL-13
Lin⁺ CD4⁺
T_H2
In situ (?)
Eosinophilopoeisis
Cationic granules
Cysteinyl leukotrienes
ROS
IL-5
IL-13
IL-4
1L-9
IL-5
IL-3
GM-CSF
CCL5
Eotaxin
CXCL8
ACTIVATION
IL-5
IL-13 expressed by ASM
Eotaxin
SURVIVAL &
STABILISATION
Sub-epithelial
fibrosis
IL-4/IL-13
CD34⁺ progenitors
RECRUITMENT
TRANS-MIGRATION
Eotaxin
IL-5
CCL5
IL-4
IL-13
MATURATION
Infiltration of leukocytes
into tissue
Eotaxin
IL-5
C/EBP α
GATA2
IL-5
IL-3
GM-CSF
MIGRATION
V-CAM1
I-CAM 1
Index to follow diagram:
stimulates
activate / process
releases
TEXT
Different stages of eosinophil biology
TEXT
Stages of airway pathogenesis
CD34
CCR3receptor
IL5α receptor
FCεRI
TSLP receptor complex
ST2 receptor
IL-5
Eotaxin


FORMATION OF FREE RADICALS
UV LIGHT
IONIZING RADIATION
SMOKING
METABOLISM
Mitochondrion
SKIN DAMAGE
INFLAMMATION
AIR POLLUTION
White blood cell
UV
(in air)


Metabolic endotoxemia
Low grade inflammation, Insulin resistance, Type 2 diabetes
Gut barrier alterations
«Dysbiosis»
Gut microbiota
Nutritional
and genetic obesity
ZO-1/Occludin

INFLAMMATION AND OBESITY



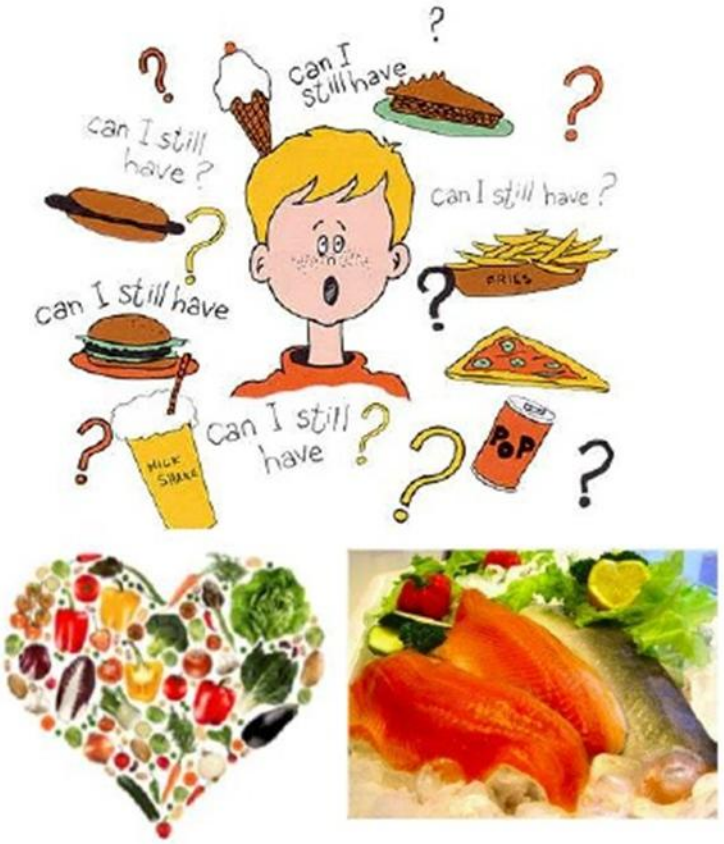


PREVENTION


CAUTION
PESTICIDE SPRAYING
IN PROGRESS
PROCEED AT OWN RISK

AVOID PROCESSED FOOD AND HIGH ANIMAL FAT FOOD.

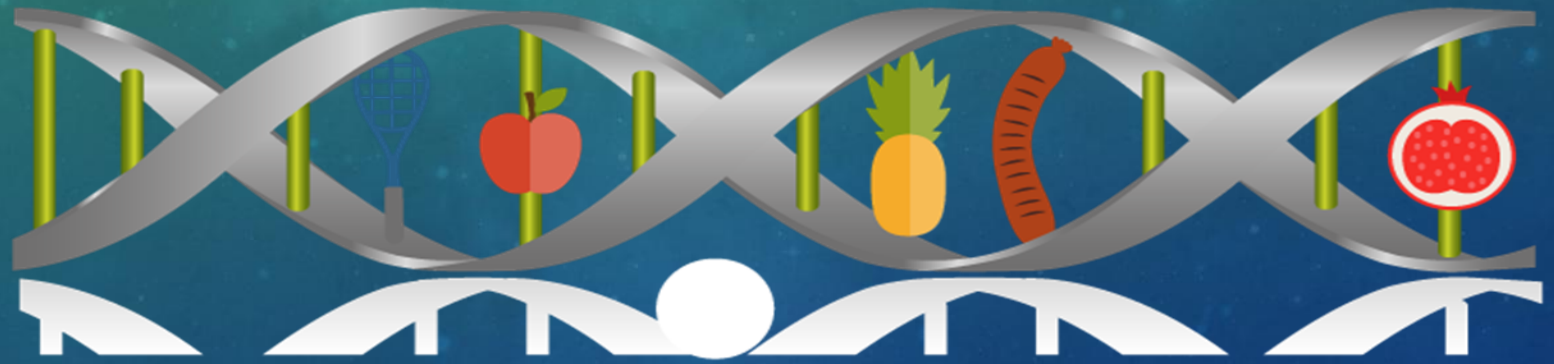
Challenge 2: What's healthy?



Thank you

Best in Health

Age well



www.boisethyroid-endocrinology.com