Endobiogeny: Personalized Medicine for All: *Applied Global Systems Biology*

Kamyar M. Hedayat, MD

President, American Society of Endobiogenic Medicine and Integrative Physiology

Co-President, Systems Biology Research Group

© 2015 Systems Biology Research Group

INTRODUCTION: WHAT IS PERSONALIZED MEDICINE?

© 2015 Systems Biology Research Group

Goals

- Distinguish two approaches to Personalized Medicine
- Learn the difference between global and non-global systems approaches to human physiology
- Learn how to personalize the treatment of Thyroiditis and Anxiety

© 2015 Systems Biology Research Group

PERSONALIZED MEDICINE: HYPE OR HOPE?

© 2015 Systems Biology Research Group

3 women divorce at menopause

Stress

- Anxiety
- MS

Stress

- Anxiety
- Hashimoto

Stress

- Joy
- UTI

© 2015 Systems Biology Research Group

Promise of Personalized Medicine

Hayes *et al. BMC Medicine* 2014, 12:37
http://www.biomedcentral.com/1741-7015/12/37

BMC Medicine

FORUM Open Access

Personalized medicine: risk prediction, targeted therapies and mobile health technology

Daniel F Hayes[1], Hugh S Markus[2], R David Leslie[3] and Eric J Topol[4]

All correspondence should be made to the journal editorial office: bmcmedicineeditorial@biomedcentral.com

Abstract

Personalized medicine is increasingly being employed across many areas of clinical practice, as genes associated with specific diseases are discovered and targeted therapies are developed. Mobile apps are also beginning to be used in medicine with the aim of providing a personalized approach to disease management. In some areas of medicine, patient-tailored risk prediction and treatment are applied routinely in the clinic, whereas in other fields, more work is required to translate scientific advances into individualized treatment. In this forum article, we asked specialists in

© 2015 Systems Biology Research Group

Foundation of a Genetic Approach

Gene "X" single protein → cells metabolism

→ tissues function

→ whole system

→ Disease Y.

Ergo: gene "X" is the cause of disease "Y"

© 2015 Systems Biology Research Group

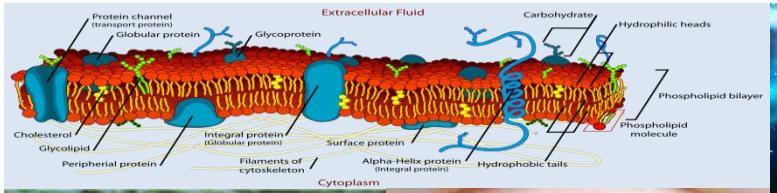
Perils of Genetic Approach

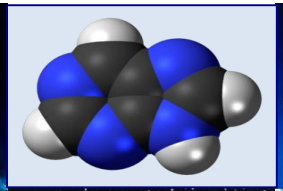
- Billions spent, very little clinical treatments
- Correlation vs. Causation
  - Retrospective studies positive[1]
  - Prospective studies non-significant[2-4]

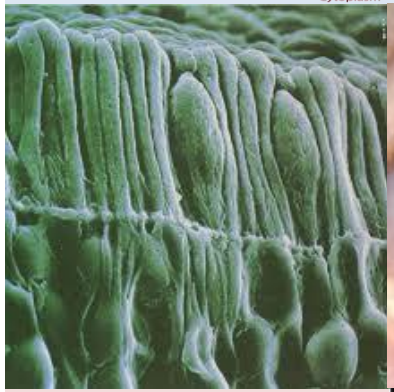
1. Iakoubova OA, Robertson M, Tong CH, et al. KIF6 Trp719Arg polymorphism and the effect of statin therapy in elderly patients: results from the PROSPER study. Eur J Cardiovasc Prev Rehabil. 2010;17(4):455-61.
2. Assimes TL, Holm H, Kathiresan S, et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and coronary artery disease in 19 case-control studies. J Am Coll Cardiol. 2010;56(19):1552-63.
3. Mathew J, Narayanan P, Sundaram R, et al. Lack of association between Glu(298) asp polymorphism of endothelial nitric oxide synthase (eNOS) gene and coronary artery disease in Tamilian population. Indian Heart J. 2008;60(3):223-7.
4. Tsantes AE, Nikolopoulos GK, Bagos PG, Vaiopoulos G, Travlou A. Lack of association between the platelet glycoprotein Ia C807T gene polymorphism and coronary artery disease: a meta-analysis. Int J Cardiol. 2007;118(2):189-96.

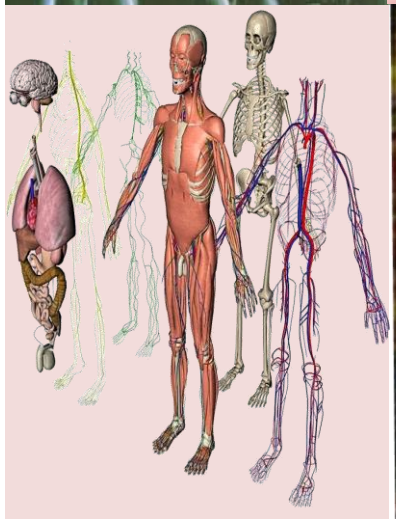
© 2015 Systems Biology Research Group

Putting *Person* in Personalized Medicine









(c) 2014 Systems Biology Research Group

INTRODUCTION TO ENDOBIOGENY

© 2015 Systems Biology Research Group

ENDOBIOGENY

Reductionism

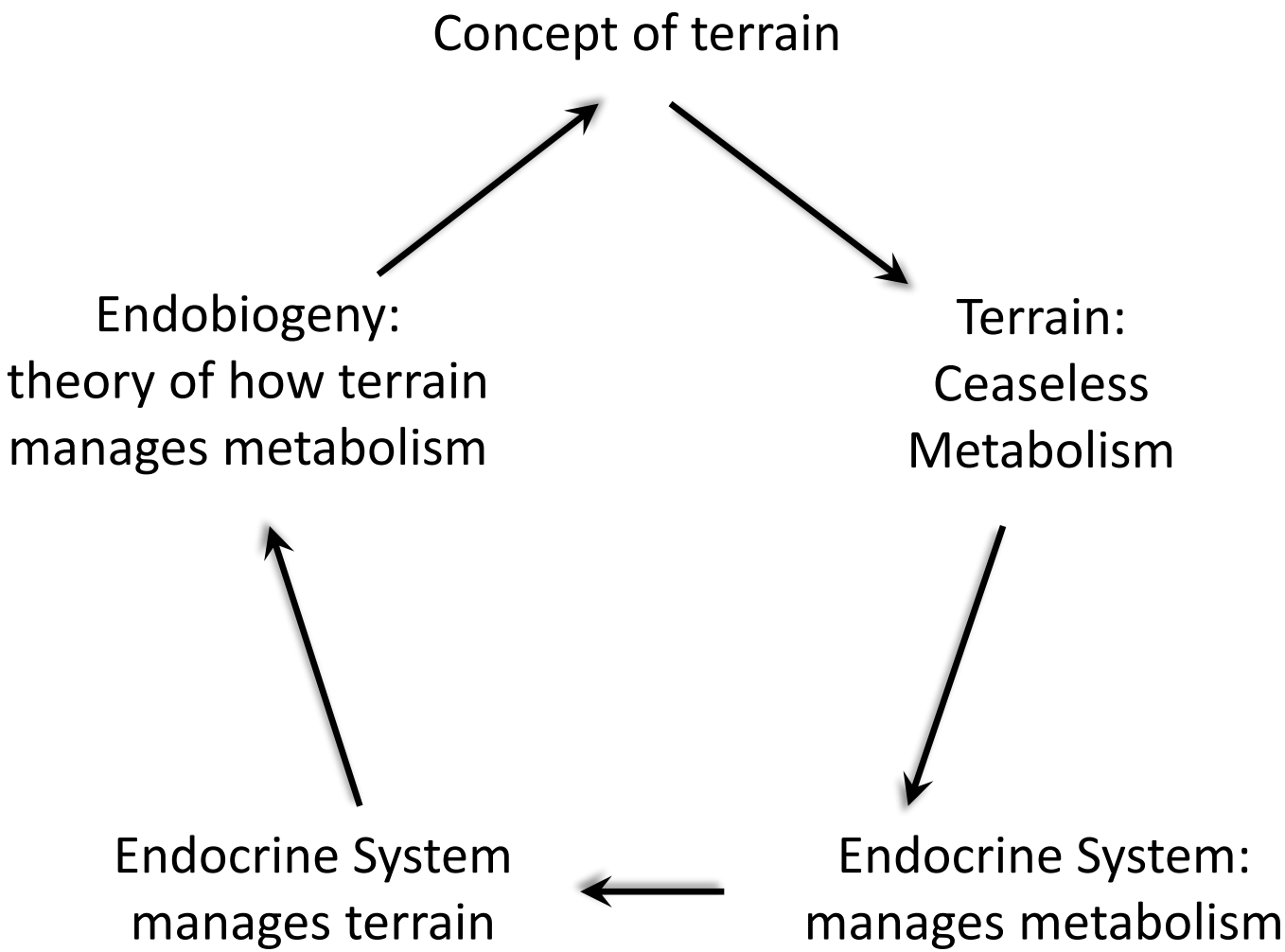
- Quantitative
- Function of the parts
- Hierarchy
- Categorical
- Separate
- Independent
- Static
- Control

Holism

- Qualitative
- Function of System
- Relationships
- Individualized
- Interconnected
- Interdependence
- Dynamic
- Creative chaos

(C) 2014 Systems Biology Research Group

Regulation of Terrain



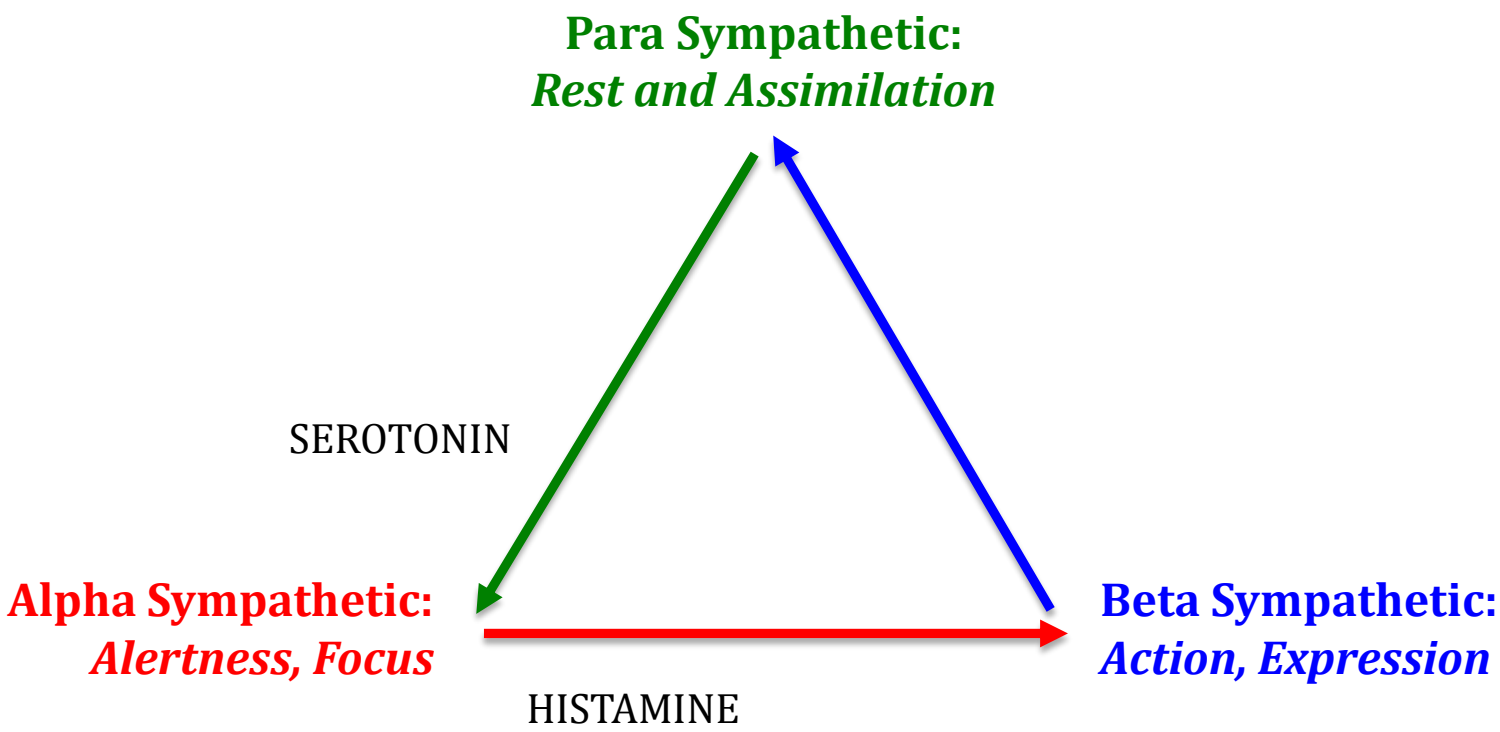
© 2015 Systems Biology Research Group

Elements of the Terrain: Metabolism

METABOLISM			
ENDOCRINE MANAGEMENT			
CATABOLISM	ANABOLISM	CATABOLISM	ANABOLISM
CRH ACTH ADRENALS	GnRH FSH LH GONADS	TRH TSH THYROID	GHRH GH PL PANCREAS
Corticotropic	Gonadotropic	Thyrotropic	Somatotropic
Nutrients	Proteins	Lipids	Lipids, Carbs

© 2015 Systems Biology Research Group

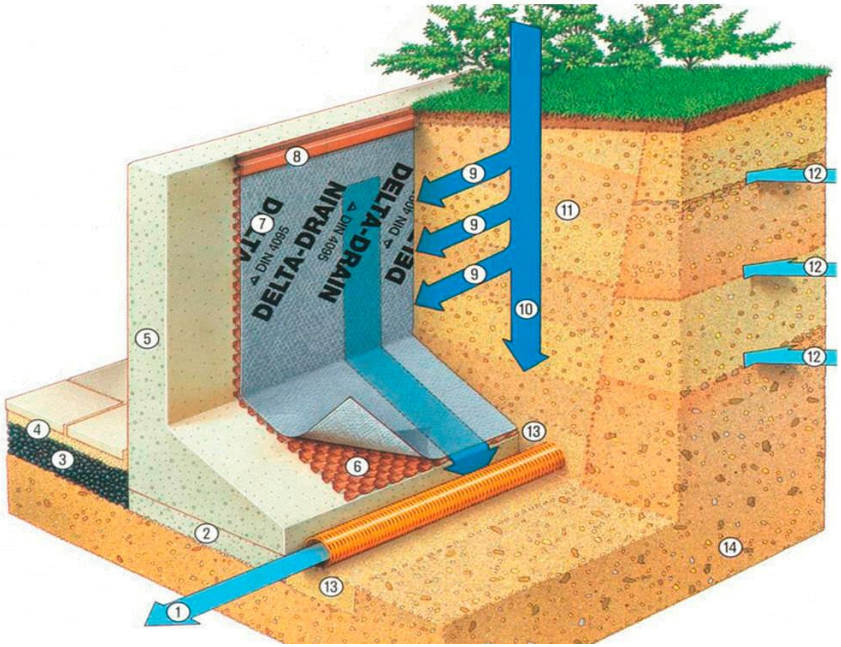
Elements of Terrain: ANS

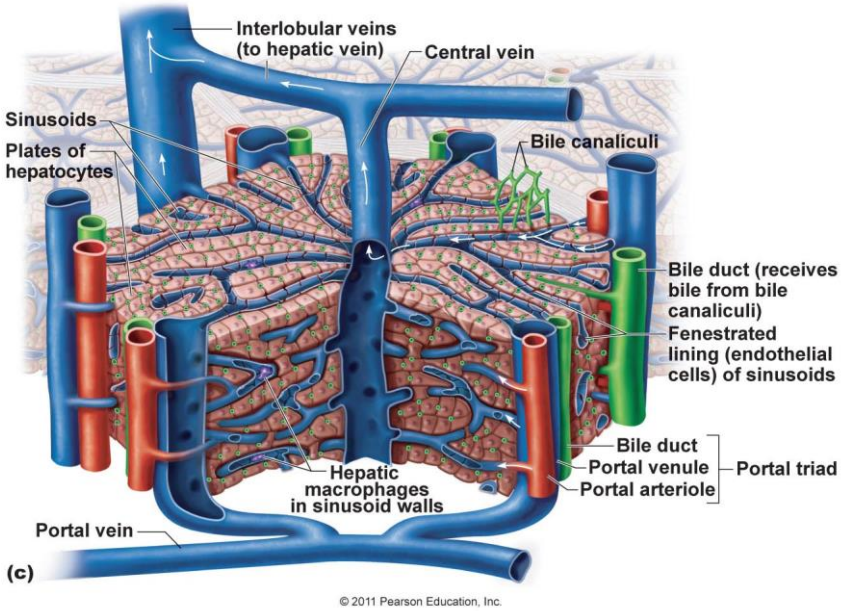


© 2015 Systems Biology Research Group

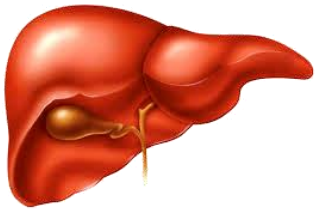
Emunctories

- an organ that drains and excretes waste products.

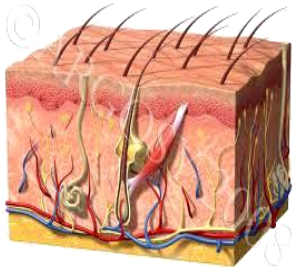


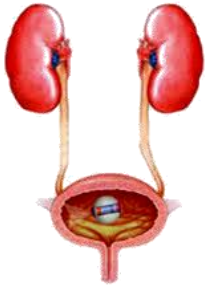


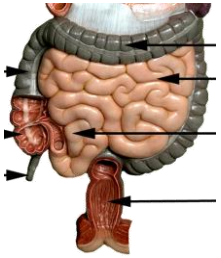
Emunctory-Endocrine relationships



CATABOLISM	CATABOLISM
CRH	TRH
ACTH	TSH
ADRENALS	THYROID
Corticotropic	Thyrotropic

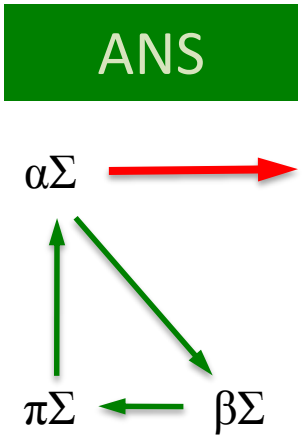




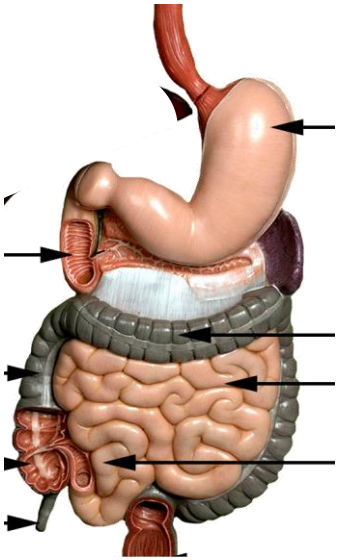


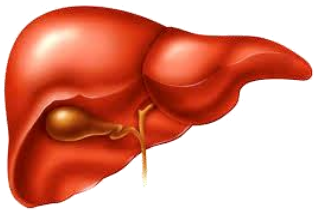
© 2015 Systems Biology Research Group

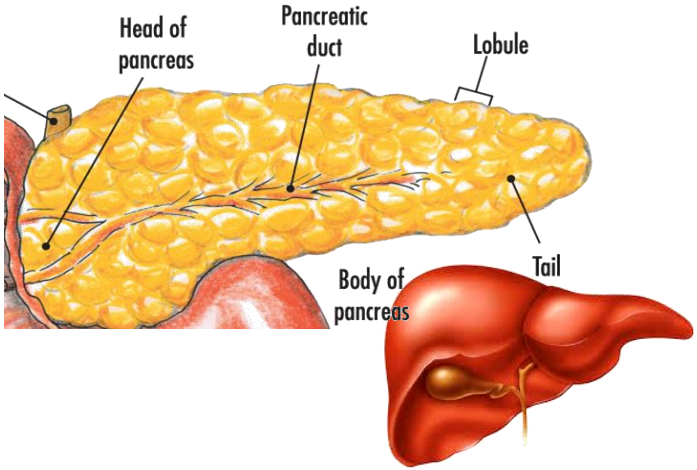
Endocrine Axes and Glands



CATABOLISM	ANABOLISM	CATABOLISM	ANABOLISM
CRH	GnRH	TRH	GHRH
ACTH	FSH LH	TSH	GH PL
ADRENALS	GONADS	THYROID	PANCREAS
Corticotropic	Gonadotropic	Thyrotropic	Somatotropic

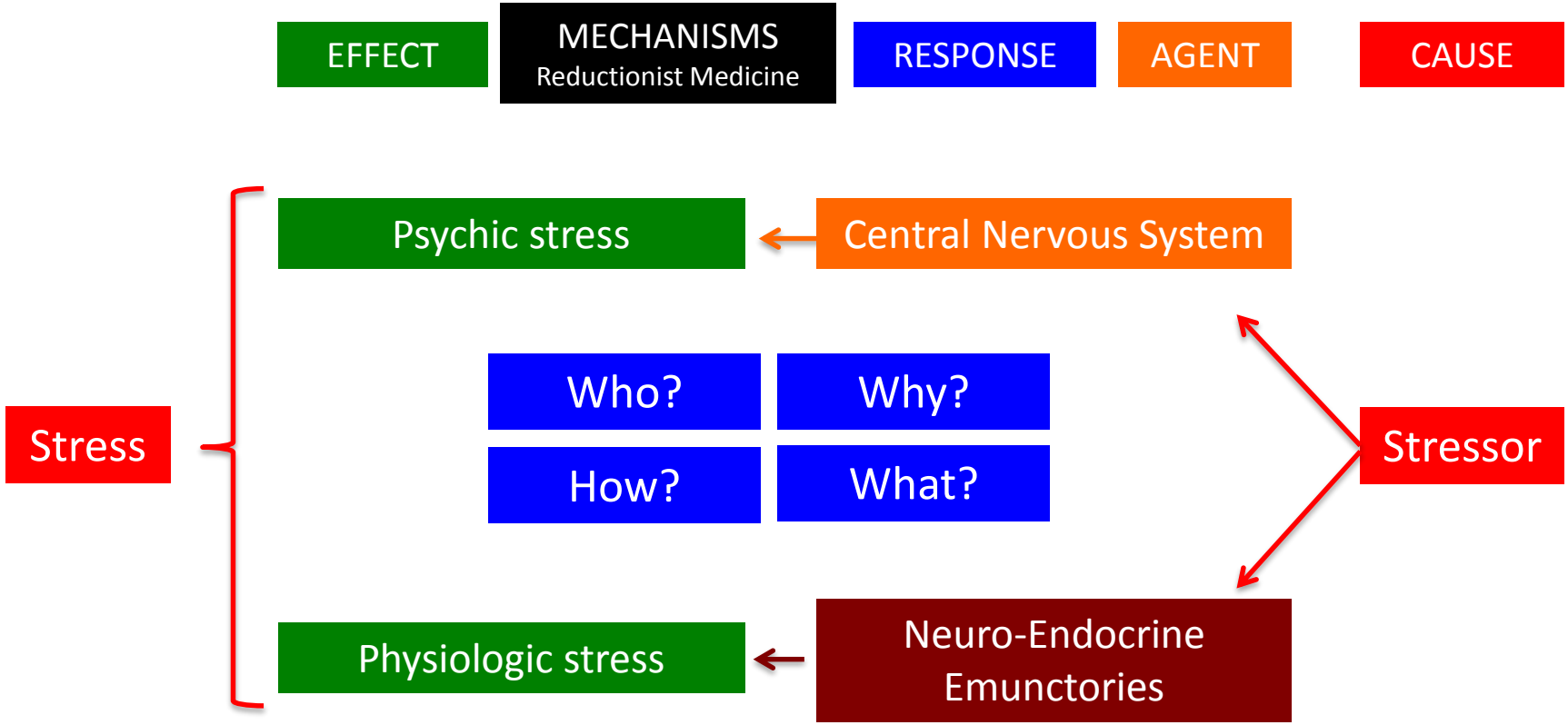






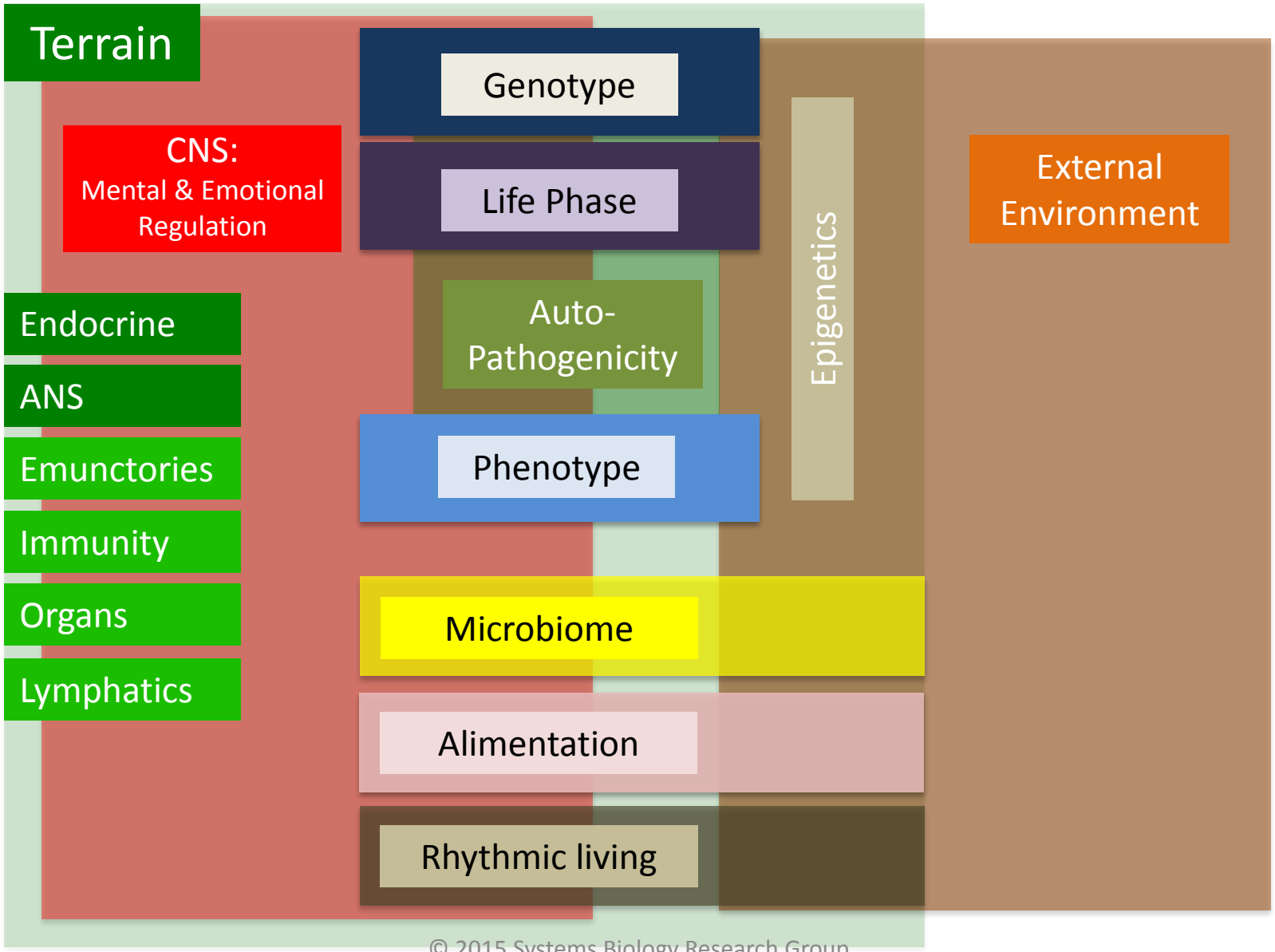
© 2015 Systems Biology Research Group

Stress: General Considerations



© 2015 Systems Biology Research Group

Global Systems Personalized Approach to Stress

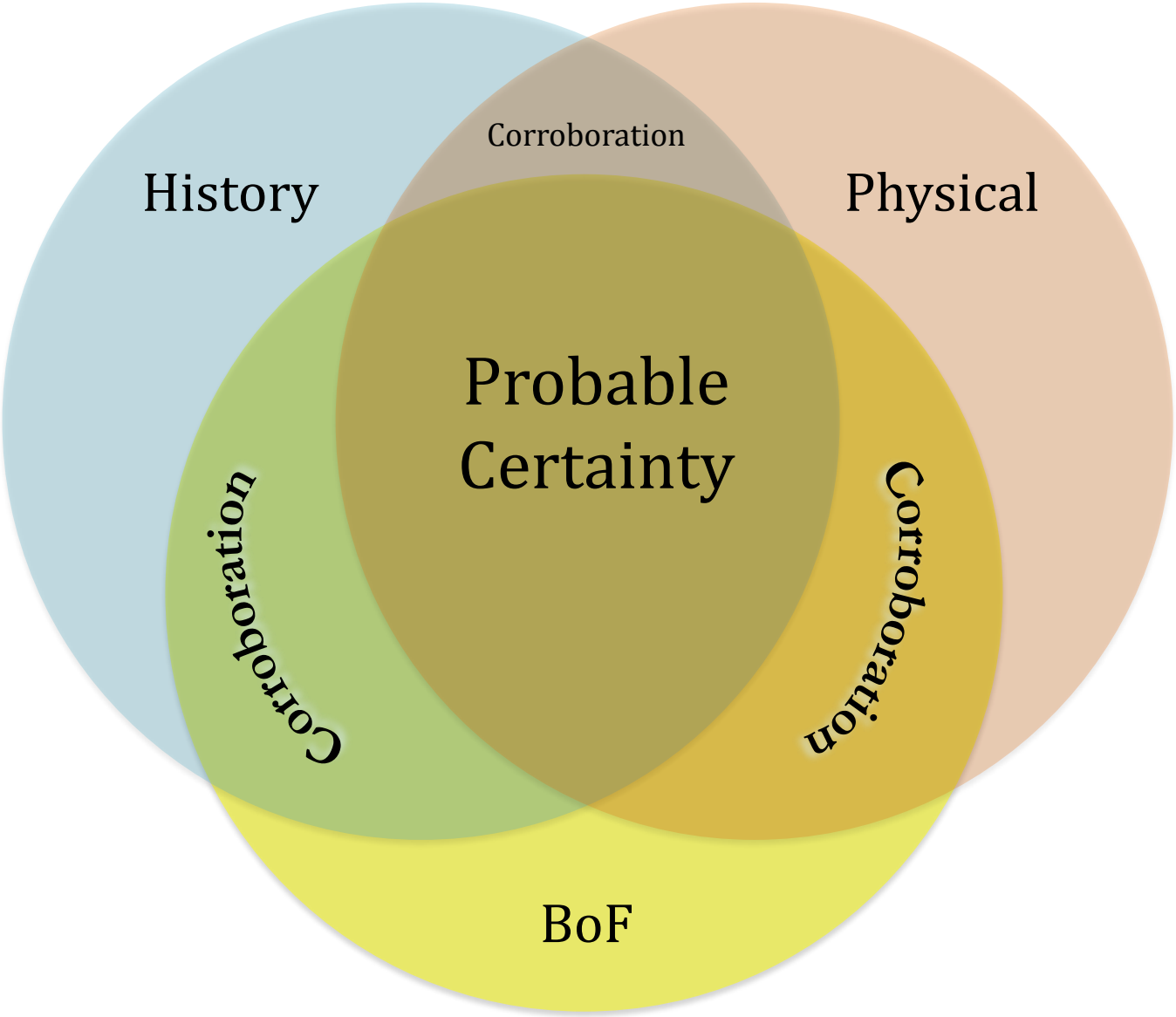


© 2015 Systems Biology Research Group

ENDOBIOGENIC APPROACH TO EVALUATION AND TREATMENT

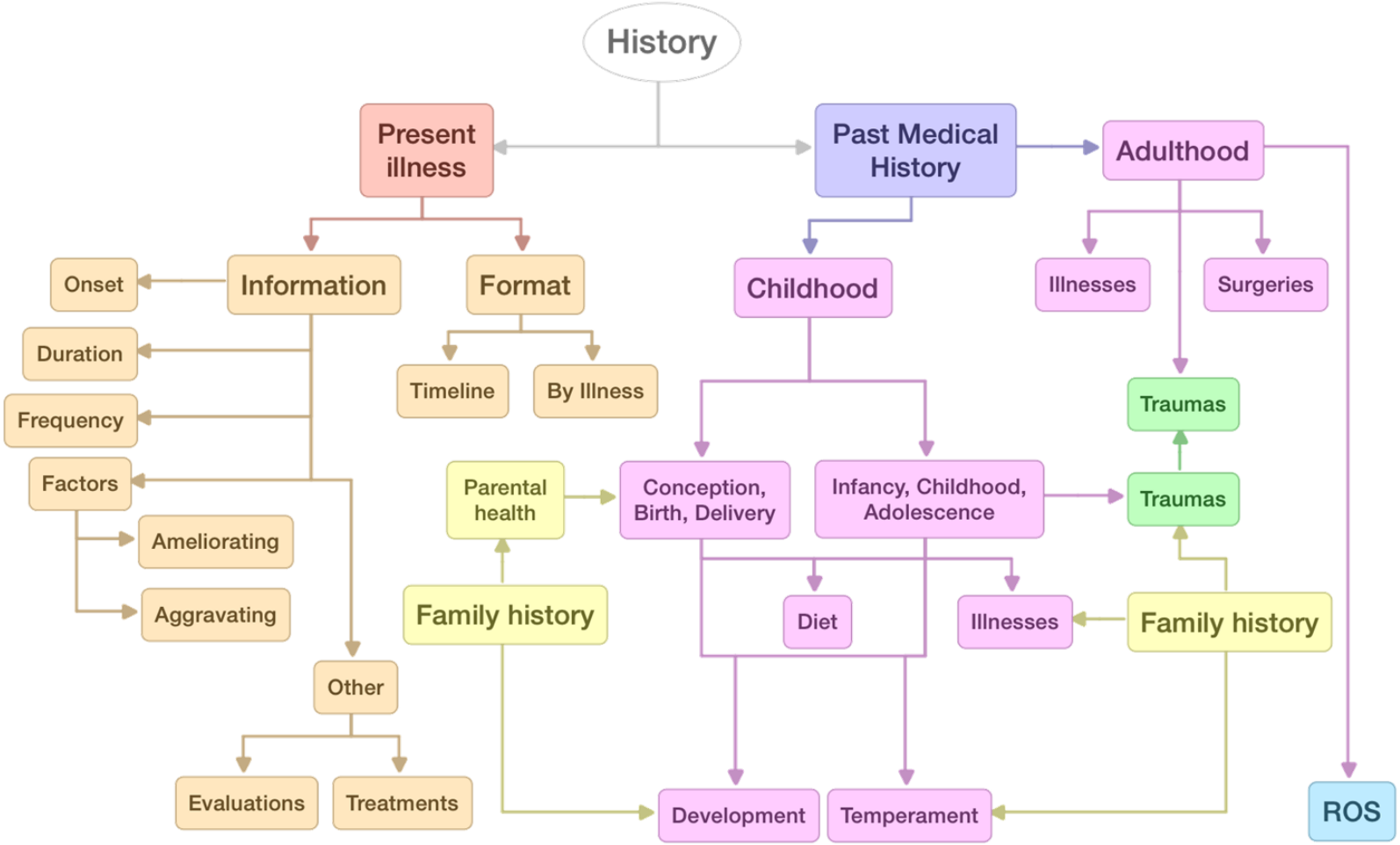
© 2015 Systems Biology Research Group

Approaching Clinical Certainty



© 2015 Systems Biology Research Group

Overview of the History

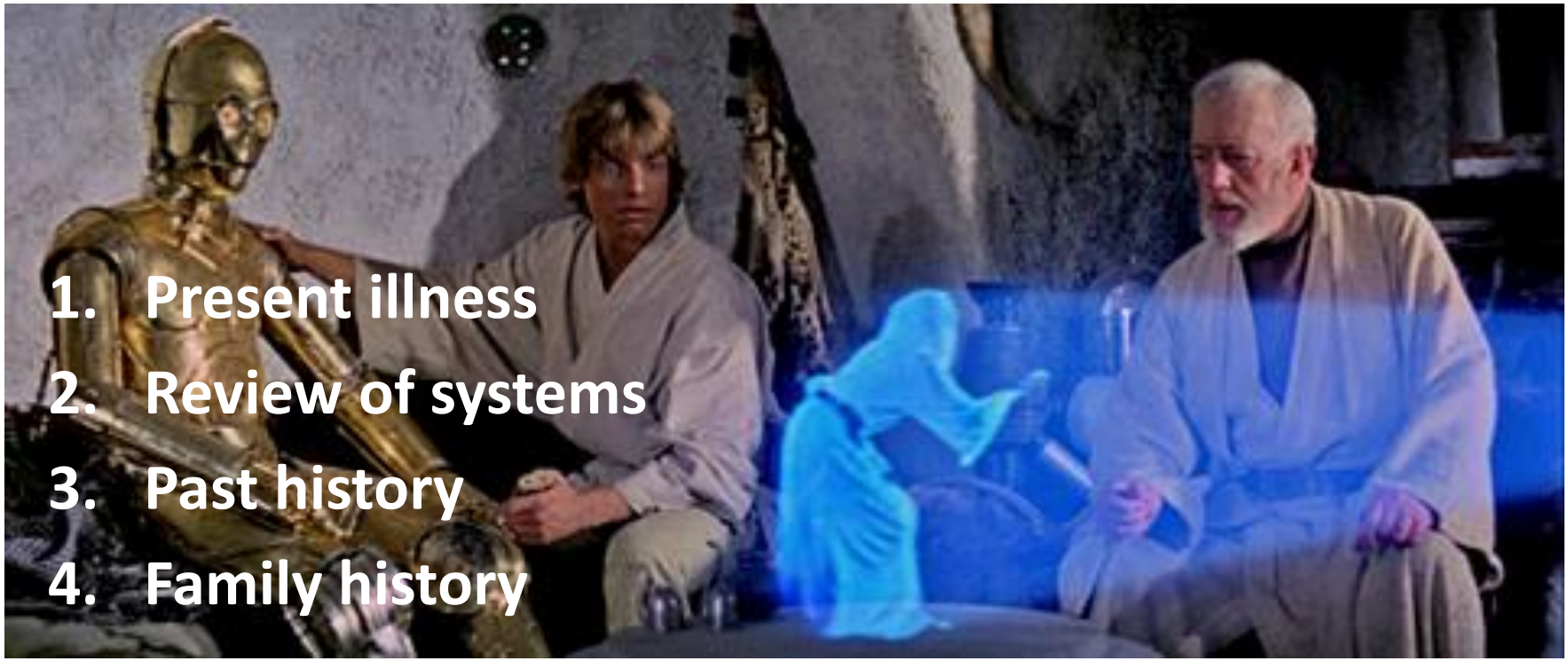


© 2015 Systems Biology Research Group

Essence of the History

The endobiogenic consultation creates a dynamic, historical, holographic and hierarchical assessment of the patient as a living being moving through space and time in constant and dynamic action and reaction to its internal and external environments.

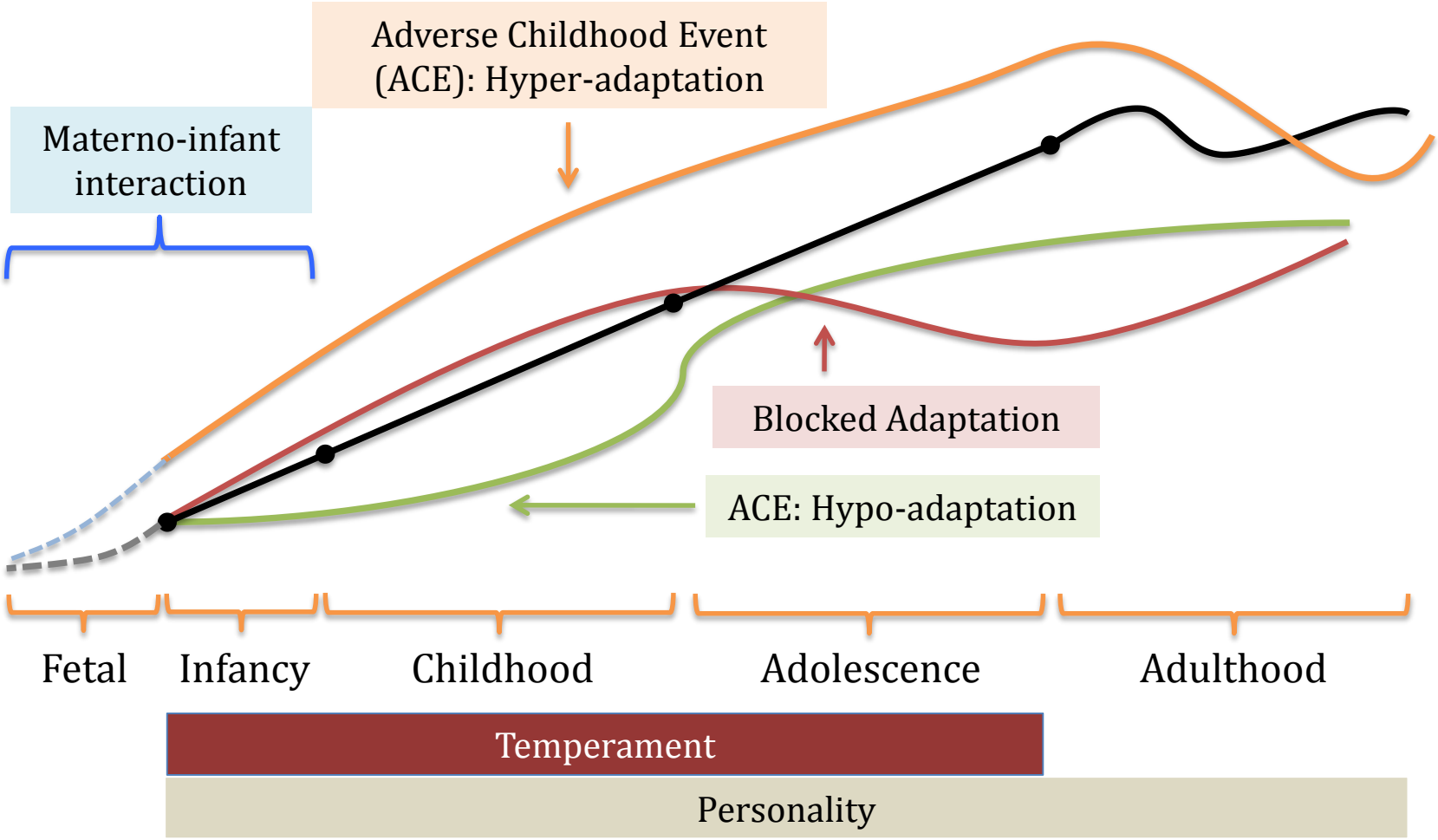
Elements of the History



1. Present illness
2. Review of systems
3. Past history
4. Family history

Call forth a story from the person seeking healing.

Neuroendocrine trajectories



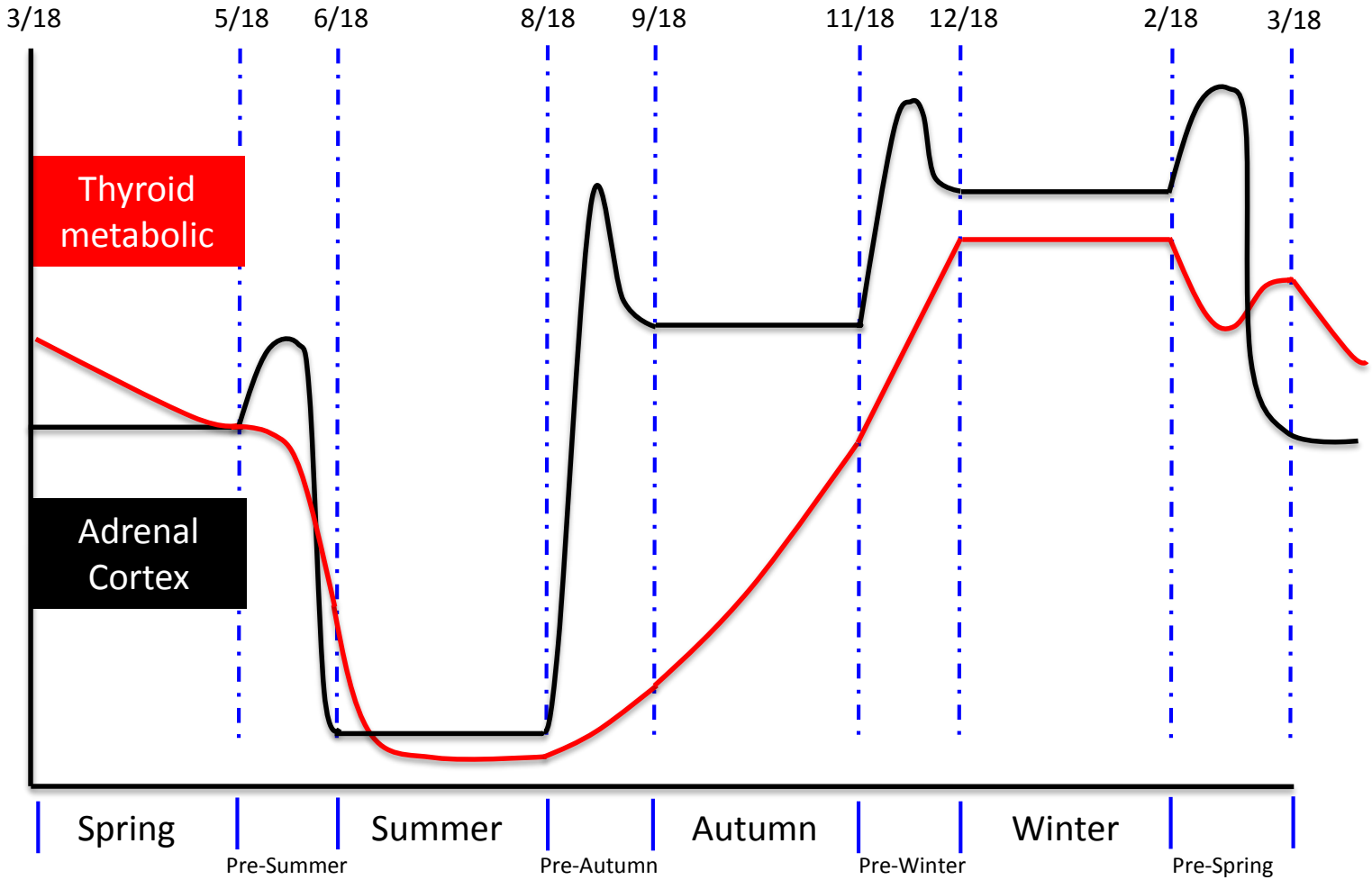
(C) 2015 Systems Biology Research Group

Matrix of PMH factors

Category	Sub-Category	FACTORS					
		Genetic	Epi-genetic	Pheno-type	Culture	Environ-ment	Geo-graphy
Childhood	Conception	◆	◆	◆		◆	
	Birth	◆	◆	◆			
	Infancy	◆	◆	◆	◆	◆	◆
	Toddlerhood	◆	◆	◆	◆	◆	◆
	Adolescence	◆	◆	◆	◆	◆	◆
Medical	N/A	◆	◆	◆			◆
Surgical	N/A	◆	◆	◆			◆
Family history	N/A	◆	◆	◆	◆	◆	◆

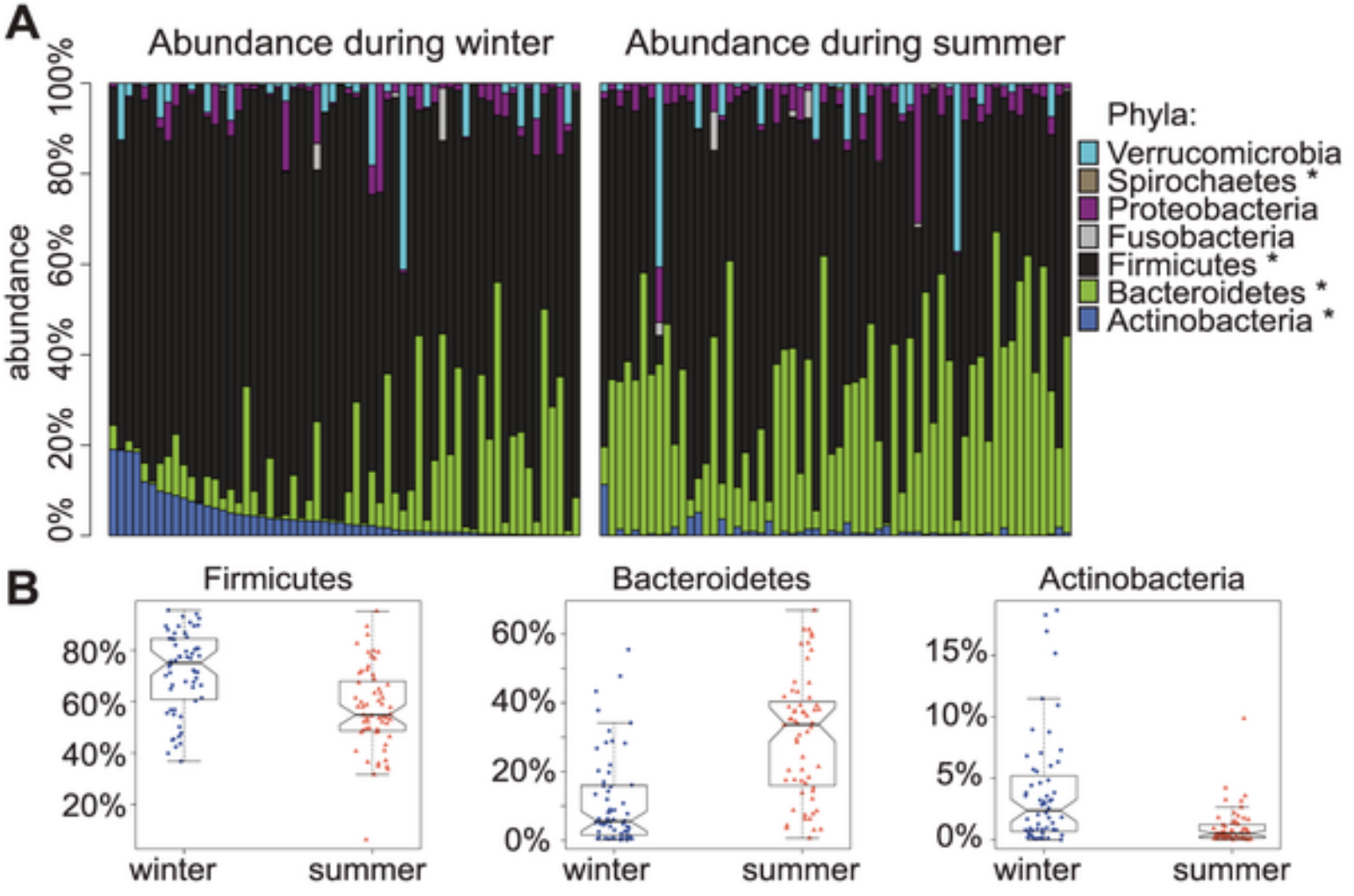
(C) 2015 Systems Biology Research Group

Seasons and Chronobiology



© 2016 Systems Biology Research Group

Figure 3. Phylum level taxa abundances differ by season.

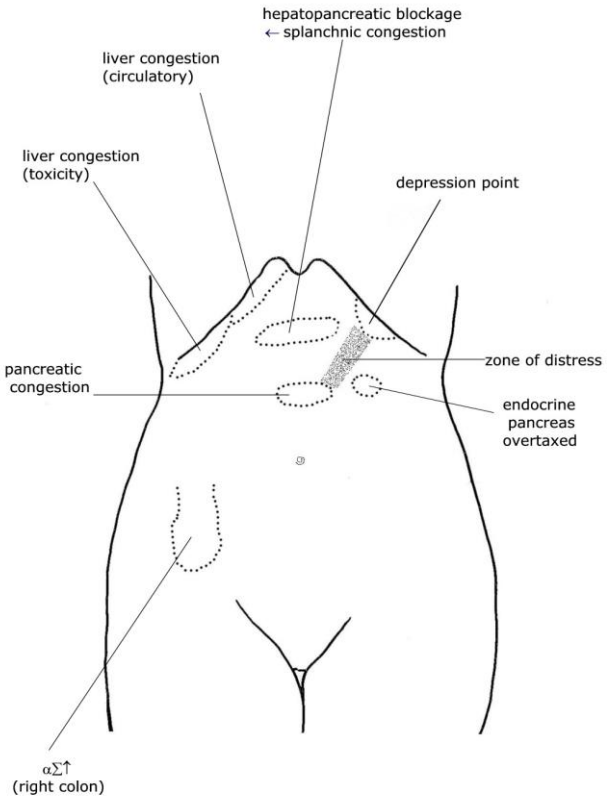


Davenport ER, Mizrahi-Man O, Michelini K, Barreiro LB, Ober C, et al. (2014) Seasonal Variation in Human Gut Microbiome Composition. PLoS ONE 9(3): e90731. doi:10.1371/journal.pone.0090731
http://journals.plos.org/plosone/article%3Fid=10.1371/journal.pone.0090731

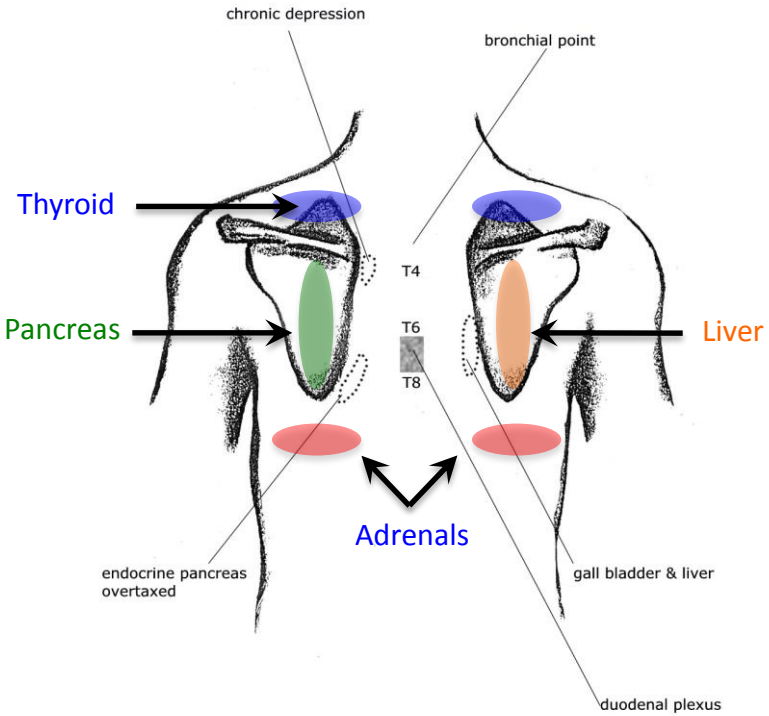
PLOS | ONE

Examination

Expert opinion only:
based on superficial referral points of viscera



Copyright © C. Duraffourd & J.C. Lapraz 2002



Copyright © C. Duraffourd & J.C. Lapraz 2002

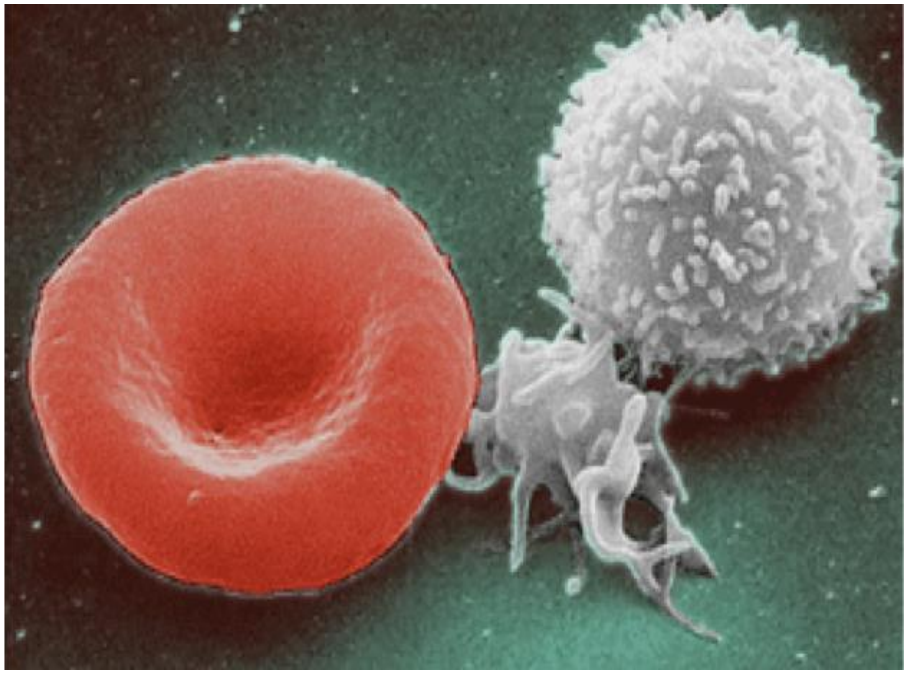
Blood Analysis: Biology of Functions

- Standard blood tests
  - Objective
  - Reproducible
- Physiologic analysis
  - Upstream/Downstream
  - Qualitative
  - Quantitative

© 2015 Systems Biology Research Group

Blood Work

Image 2: (left to right) Erythrocytes, Thrombocytes, Leukocytes



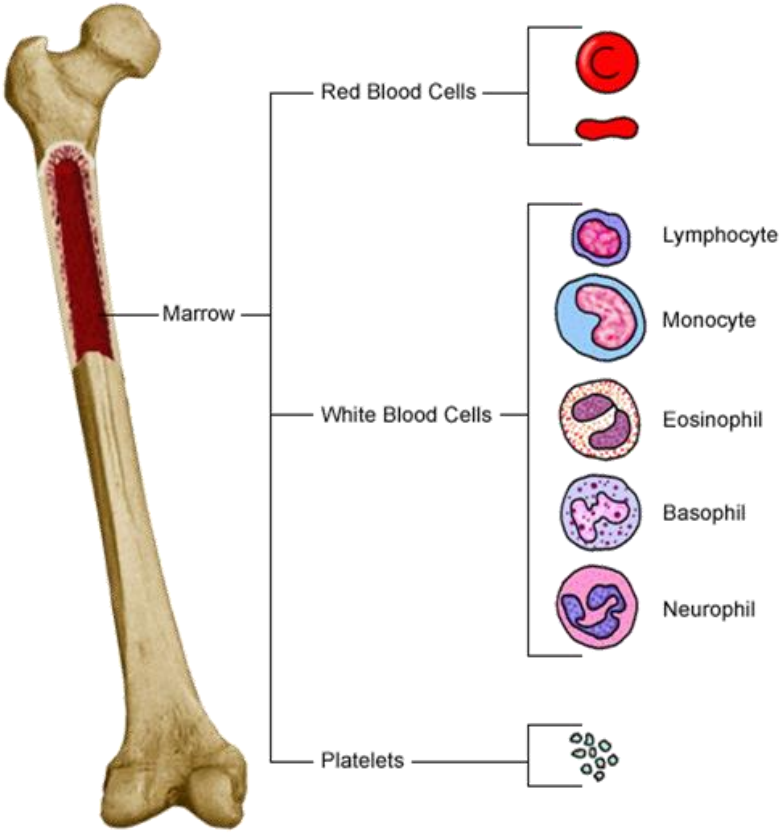


Table 1: Biomarkers

	Origin	Biomarker
70% bone and blood	Bone Marrow	Red blood cell
		White blood cell, total
		Neutrophil
		Lymphocytes
		Eosinophils
		Monocytes
		Basophils
		Hemoglobin
		Platelets
	Marrow-Blood interaction	Erythrocyte sedimentation rate
	Bone Stroma Enzymes	Osteocalcin
		Alkaline phosphatase bone isoenzyme
30% other	General Enzymes	Lactate dehydrogenase
		Creatine phosphokinase
	Endocrine: Pituitary	Thyroid stimulating hormone
	Electrolytes	Potassium
		Calcium, total serum

Upstream/Downstream: Direct

UPSTREAM

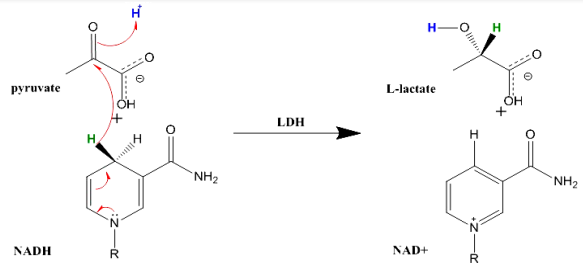
DOWNSTREAM

T4, T3

??

Increased Oxidative Demand

Cell



Reduced Oxidative Demand

↑ LDH

↓ LDH

© 2015 Systems Biology Research Group

Upstream/Downstream: Inverse

UPSTREAM

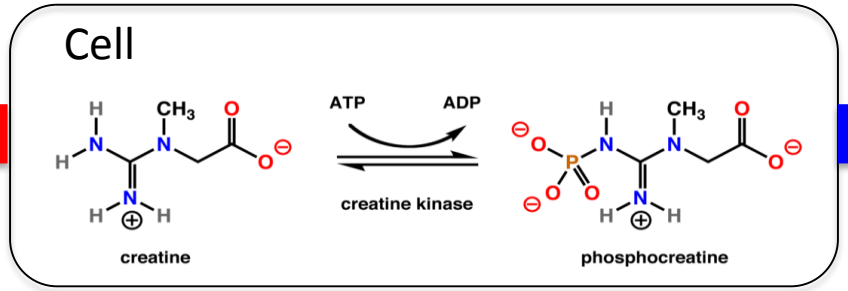
DOWNSTREAM

T4, T3

??

Efficient Thyroid Metabolic

Inefficient Thyroid Metabolic



↓ CK

↑ CK

© 2015 Systems Biology Research Group

Direct ratio

Thyroid Metabolic Index

- Metabolic activity of thyroid hormones

= LDH / CK = 3.5-5.5

© 2015 Systems Biology Research Group

Clinical Observations

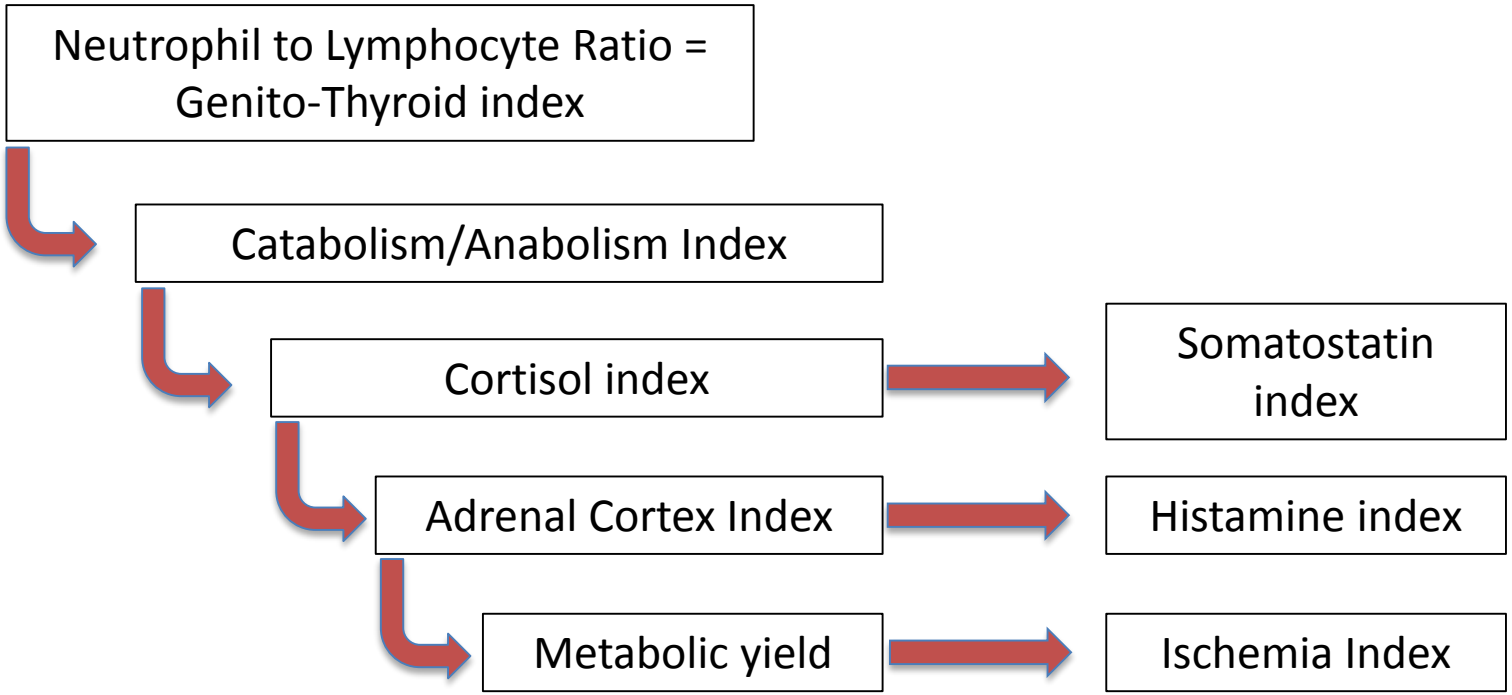
Condition	LDH	CPK	Ratio
Hyperthyroidism	233.80	88.37	2.65
Sub-clinical Hyperthyroidism	227.81	105.98	2.15
Normal controls	202.85	102.19	1.99
Sub-clinical hypothyroidism	340.38	179.8	1.89
Hypothyroidism	421.00	389.90	1.08

Modified from McGrowder, DA et al., Nig J Clin Pract, 14(4), 2011

© 2015 Systems Biology Research Group

Endobiogenic Indices: Higher orders of observation

Simple direct → Metaindices



© 2015 Systems Biology Research Group

What is the patient's diagnosis?

CBC With Differential/Platelet

WBC	4.4
RBC	4.62
Hemoglobin	13.8
Hematocrit	40.8
MCV	88
MCH	29.9
MCHC	33.8
RDW	14.0
Platelets	218
Neutrophils	59
Lymphs	32
Monocytes	6
Eos	2
Basos	1
Neutrophils (Absolute)	2.6
Lymphs (Absolute)	1.4
Monocytes(Absolute)	0.3
Eos (Absolute)	0.1
Baso (Absolute)	0.0
Immature Granulocytes	0
Immature Grans (Abs)	0.0

Comp. Metabolic Panel (14)

Glucose, Serum	92
BUN	8
Creatinine, Serum	0.83
eGFR If NonAfricn Am	94
eGFR If Africn Am	108
BUN/Creatinine Ratio	10
Alkaline Phosphatase, S	50
AST (SGOT)	18
ALT (SGPT)	12

Lipid Panel

Cholesterol, Total	156
Triglycerides	74
HDL Cholesterol	57
Comment	
According to ATP-III Guidelines, HDL- negative risk factor for CHD.	
VLDL Cholesterol Cal	15
LDL Cholesterol Calc	84

Alk Phos Isoenzyme

Liver Fraction:	56
Bone Fraction:	28
Intestinal Frac.:	16

Thyroxine (T4) Free, Direct, S

T4,Free(Direct)	1.19

CEA 0.7
Roche ECLIA met

CA 19-9 10
Roche ECLIA methodology

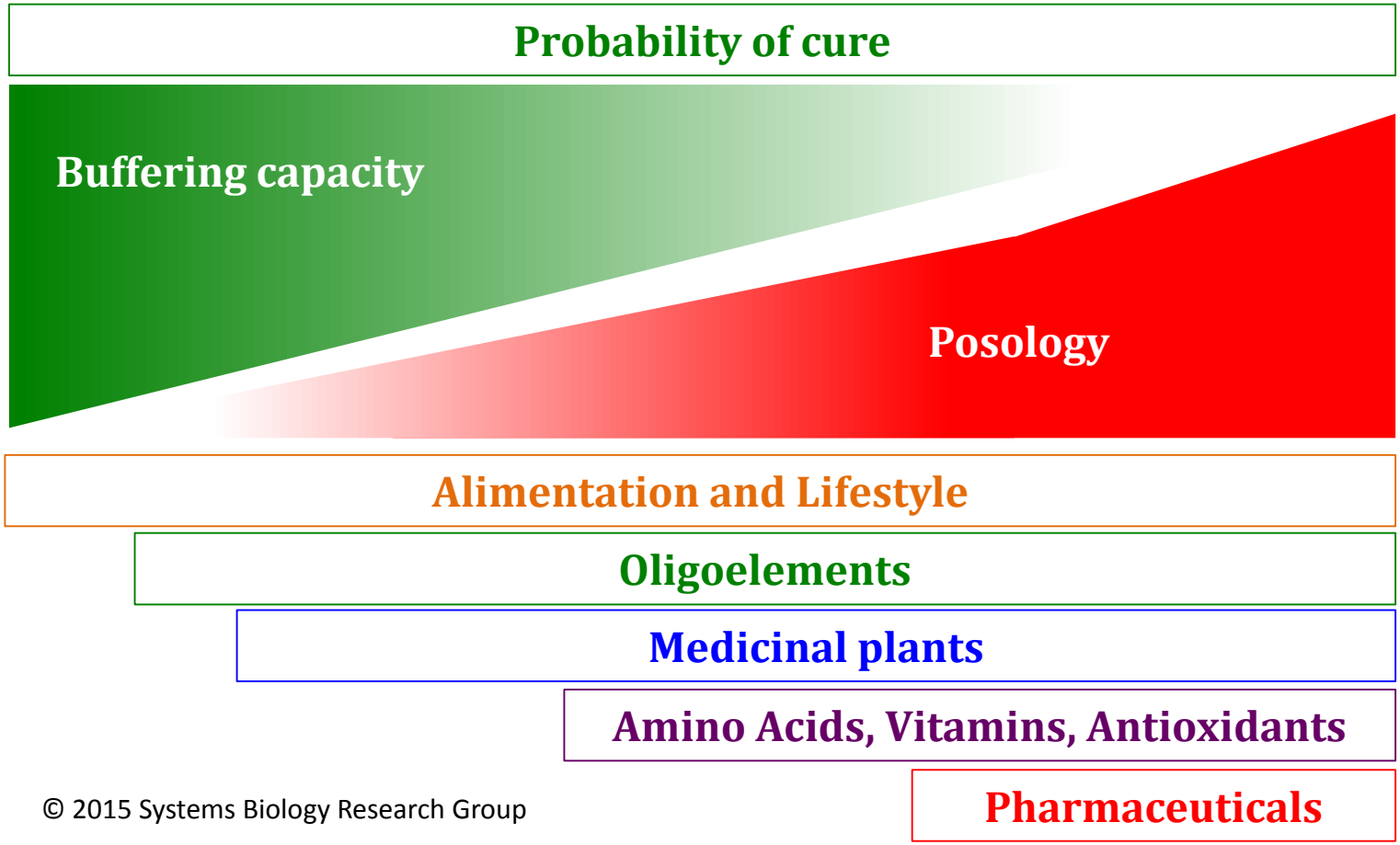
TSH 2.140

Osteocalcin, Serum 16.1
Pre-men
Post-me

Phosphorus, Serum	3.4
LDH	123
Sedimentation Rate-Westergren	2
Creatine Kinase,Total,Serum	86
Vitamin B12	893
Magnesium, Serum	1.9
Triiodothyronine,Free,Serum	2.7

© 2015 Systems Biology Research Group

Therapeutics



© 2015 Systems Biology Research Group

Activity of *Salvia officinalis* (Sauge)

METABOLISM

ANS

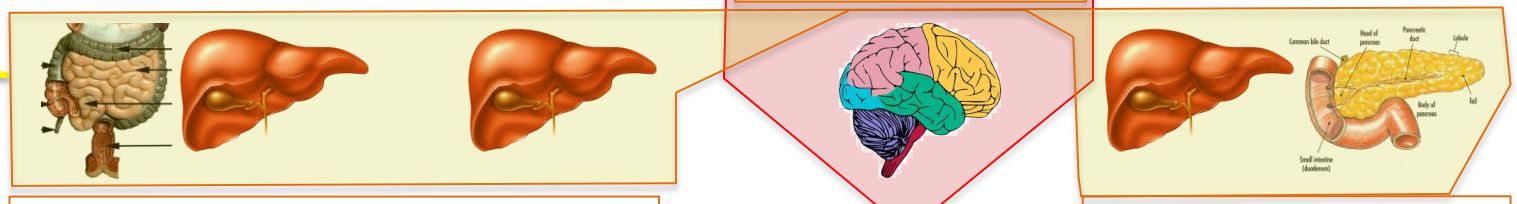
ENDOCRINE MANAGEMENT

CATABOLISM	ANABOLISM	CATABOLISM	ANABOLISM
CRH	GnRH	TRH	GHRH
ACTH	FSH LH	TSH	GH PL
ADRENALS	Estrogens	THYROID	PANCREAS
Corticotropic	Gonadotropic	Thyrotropic	Somatotropic

αΣ

πΣ

βΣ



Digestion, Metabolism, Drainage

Memory, Mood

Inflammation, Mucous

© 2015 Systems Biology Research Group

Global Systems Approach to Personalized Medicine

SCALE

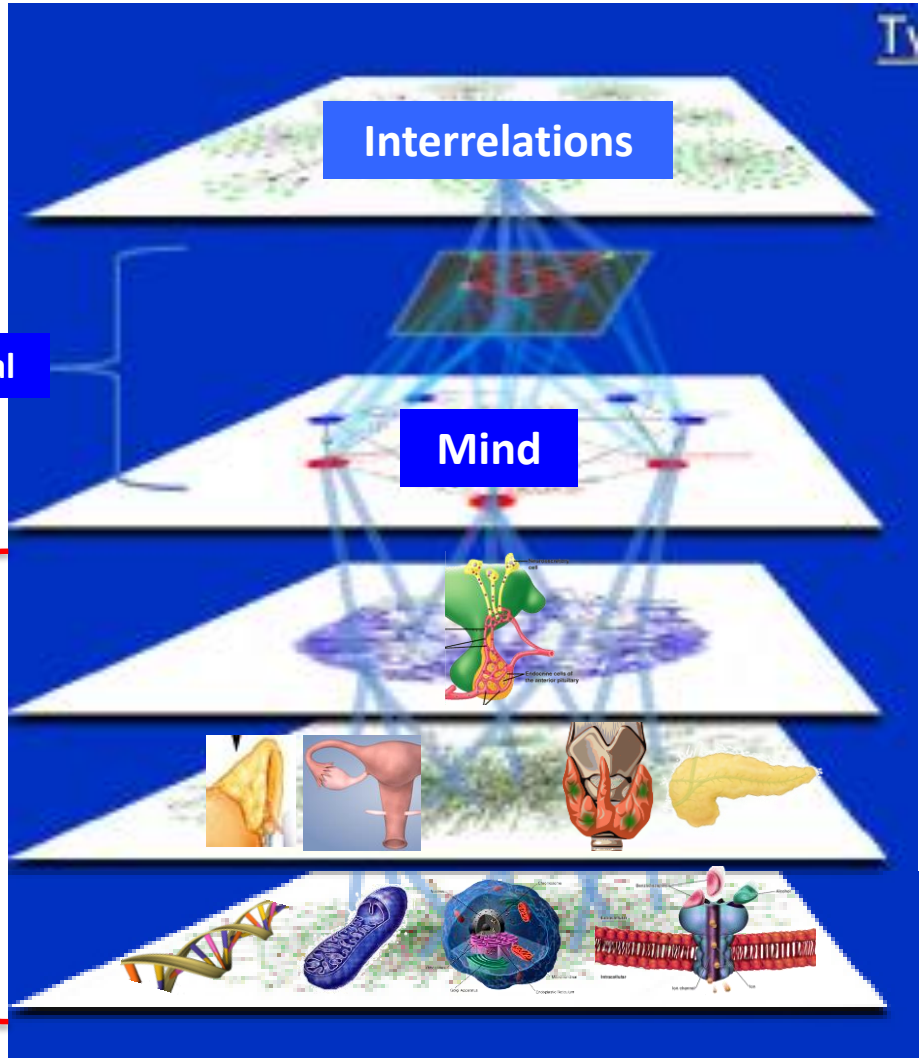
$>10^0$m: Macroscopic
- Cosmobiologic
- Symbiotic
- Social

Phenomenological

10^{-3}-10^{-1}m: Mesoscopic
- Organism
- Organs
- Tissues

Biological

10^{-6}-10^{-3}m: Microscopic
- Cellular
- Subcellular
- DNA



Modified from Looijestijn et. al.

© 2016 Systems Biology Research Group

PERSONALIZED MEDICINE: CASE STUDY

© 2015 Systems Biology Research Group

Case Study

- 55 yo female, post menopausal
- CC: Hashimoto's thyroiditis, post divorce at 48
- Other:
  - Anxiety
  - Poor sleep: intense dreams
  - Mucous congestion with dairy
  - Pre-diabetic (HgA1c 6.2%)

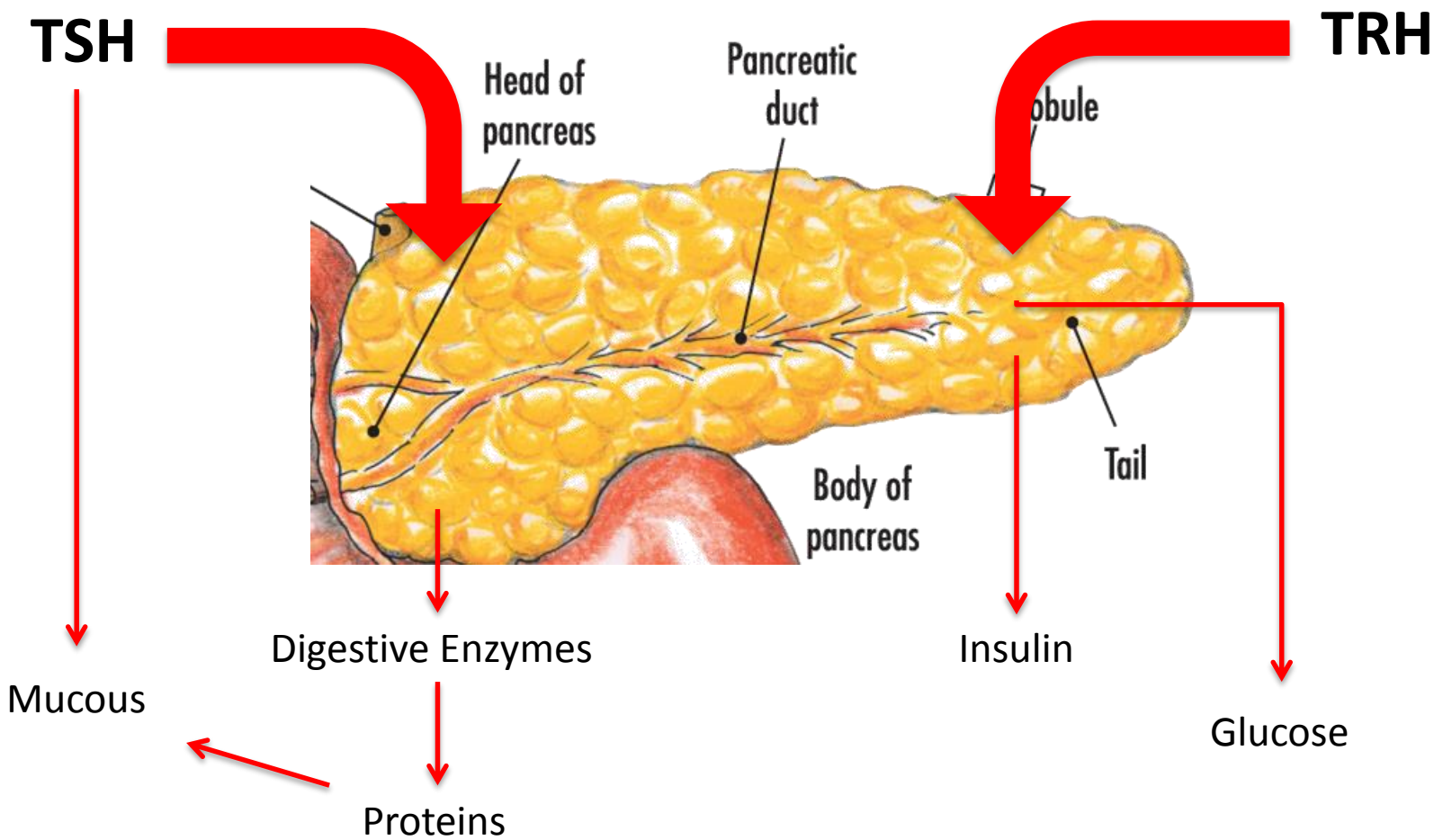
© 2015 Systems Biology Research Group

Understanding Symptoms

Symptom	TRH	TSH	Pancreas
Anxiety with tremors	↑		
Intense Dreams	↑		
Pre-diabetic	↑		Endocrine
Mucous with dairy		↑	Exocrine

© 2015 Systems Biology Research Group

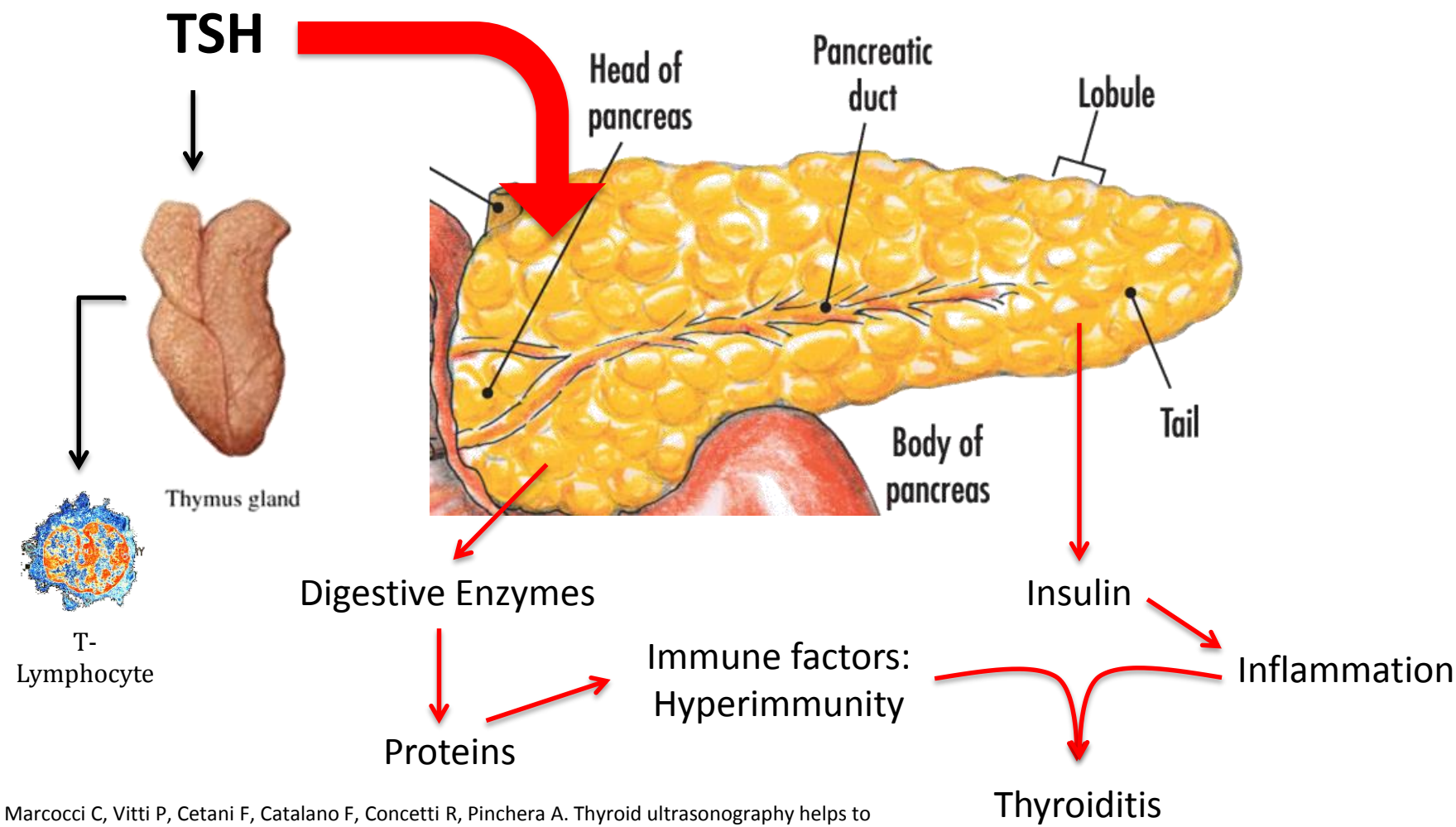
Thyrotropic Axis and Pancreas



1. Erle DJ, Sheppard D. The cell biology of asthma. The Journal of cell biology 2014;**205(5):621-31.**

© 2015 Systems Biology Research Group

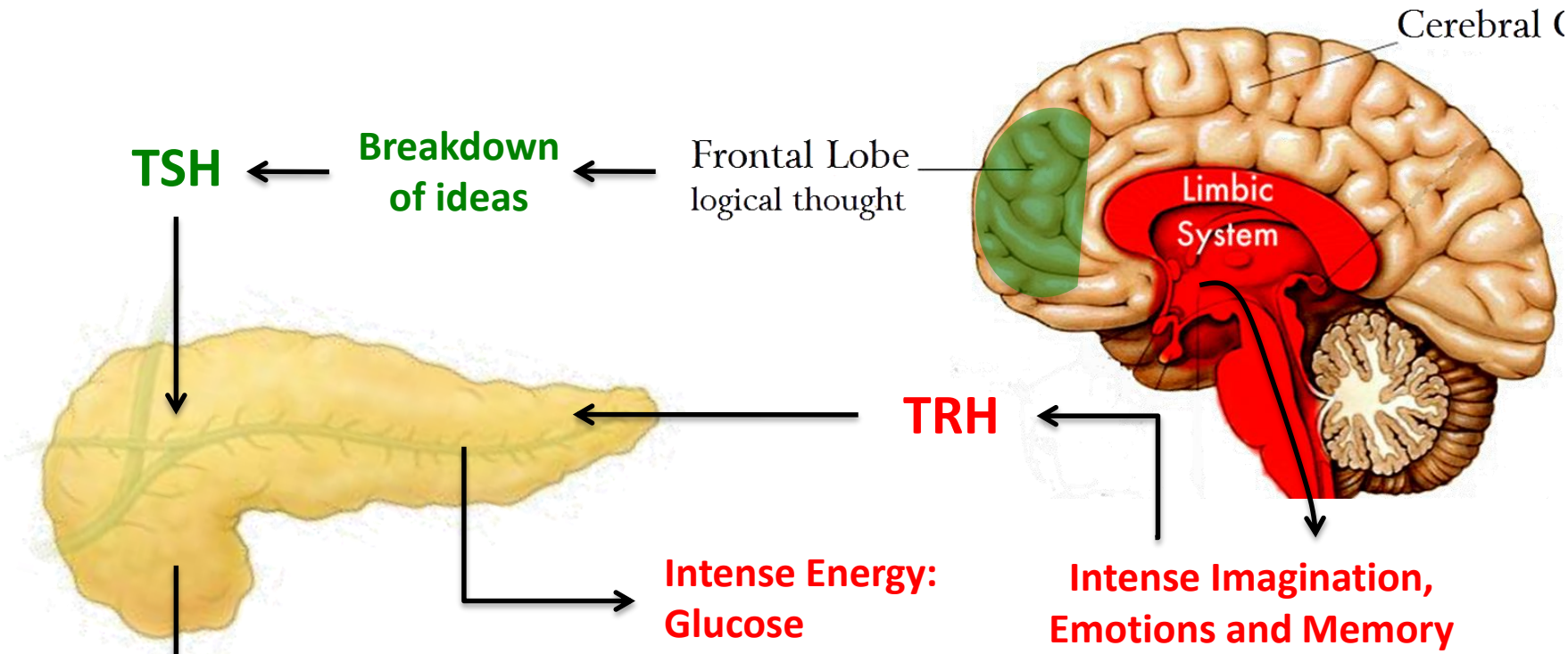
Pancreas and Immunity



Marcocci C, Vitti P, Cetani F, Catalano F, Concetti R, Pinchera A. Thyroid ultrasonography helps to identify patients with diffuse lymphocytic thyroiditis who are prone to develop hypothyroidism. *The Journal of clinical endocrinology and metabolism. 1991;72(1):209-213.*

© 2015 Systems Biology Research Group

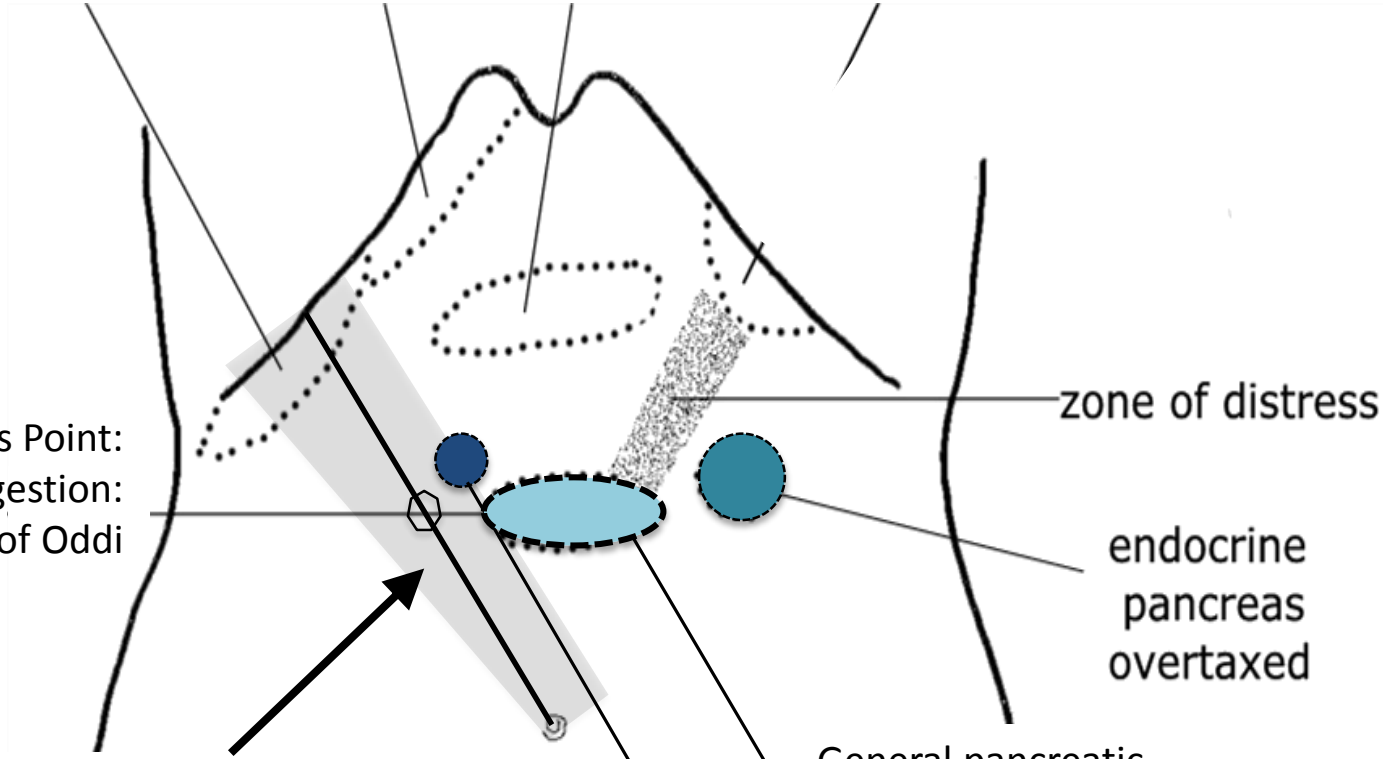
Exocrine Pancreas-CNS 2



Gary KA et al. The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. *The Journal of pharmacology and experimental therapeutics. 2003;305(2):410-416.*

© 2015 Systems Biology Research Group

Expert opinion only:
based on superficial referral points of viscera



© 2016 Systems Biology Research Group

Treatment

Symptom	TRH	TSH	Pancreas
Anxiety with tremors	Motherwort		GABA, 50 mg TID
Intense Dreams	Motherwort		GABA, 50 mg TID
Pre-diabetic	Motherwort		GABA, 50 mg TID
Mucous with dairy		Milky Oat	Milky Oat Avoid Dairy, Gluten

© 2015 Systems Biology Research Group

Sample prescriptions GABA[1,2] 50 mg TID +

Tincture

- Motherwort MT 60 ml
- Milky oat MT 60 ml
- Lavender EO 4 ml
- DOSE:
  - 2 ml with breakfast
  - 2 ml with dinner,
  - 4 ml qHS

Tisane (Medicinal Tea)

- Motherwort 8 oz
- Milky oat 4 oz
- Passionflower 4 oz
  - Mix together
  - Steep 1 tsp in 1 cup water
- DOSING
  - Breakfast: 10 minute steep
  - Lunch: 10 min steep
  - Bedtime: 15 min steep

1. Boonstra E et. al. Neurotransmitters as food supplements: the effects of GABA on brain and behavior. *Frontiers in psychology. 2015;6:1520.*
2. Steenbergen L et. al. gamma-Aminobutyric acid (GABA) administration improves action selection processes: a randomised controlled trial. *Scientific reports. 2015;5:12770.*

© 2015 Systems Biology Research Group

Leonurus cardiaca (Motherwort)

- **Parts used**: Whole plant
- **Galenic**: MT, DE, bulk herb
- **Summary:**
  - Anxiety
  - Insomnia
  - Explosive anger
  - Dysrhythmias
  - Blood sugar disturbance

© 2016 Systems Biology Research Group

Leonurus cardiaca (Motherwort)

Actions: ENDO

- **Thyroid:**
  - TRH antagonist
  - TSH antagonist
- **Cortico:**
  - Inhibits cortisol
- **NEURO:**
  - CNS sedative
  - α-sympatholytic
  - beta-blocker

- **CV:**
  - Cardiosedative
  - Antiarrhythmic
  - Hypotensive
  - Bradycardic
  - Inotrope (+)
  - Chronotrope (-)
  - Bathmotrope (-)

1. Ovanesov KB et. al. [Effects of melatonin and motherwort tincture on the emotional state and visual functions in anxious subjects]. *Eksp Klin Farmakol.* 2006;69(6):17-19.
2. Wojtyniak K et. al. Leonurus cardiaca L. (motherwort): a review of its phytochemistry and pharmacology. *Phytotherapy research : PTR. 2013;27(8):1115-1120.*

© 2016 Systems Biology Research Group

Avena sativa (Milky oat)

- **Part used:**
  - Fruit, Aerial parts, Seeds
- **Galenic:** MT, DE, Bulk herb
- **Summary:**
  - Thyroid imbalances
  - Estrogen-Thyroid imbalances
  - Digestive disorders
  - ENT disorders

© 2016 Systems Biology Research Group

Avena sativa (Milky oat)

ACTION: ENDO:

- **Thyroid:**
  - Thyroid stimulant (T4, T3)
  - Reduces TSH by feedback regulation
- **Gondotropic**
  - **S**timulates ovaries FSH-E2 efficiency
  - Mild LH stimulant
- **Gonado-Thyrotropic**
  - Regulates the thyroid activity to the needs of estrogen
- **Somatotropic**
  - Endocrine pancreas regulation, indirect

Agradi E, Vegeto E, Sozzi A, Fico G, Regondi S, Tome F. Traditional healthy Mediterranean diet: estrogenic activity of plants used as food and flavoring agents. *Phytotherapy research : PTR. 2006;20(8):670-675.*

© 2016 Systems Biology Research Group

Avena sativa (Milky oat)

ACTION:

- **Metabolic:** hypoglycemant, hypolipemiant
- **GI: Pancreas, Exo:** carbohydrate metabolism
- **Lymph:** lymphatic drainage
- **CV:** anti-atherosclerotic
- **ANS/NEURO:** Neuro-Regulatory
- **RENAL:** Diuretic

© 2016 Systems Biology Research Group

Follow up

- D1: Sleep quality improved
- 1 mo: Reduced anxiety, still daily
- 2 months: Dreams less intense
- 3 months:
  - Tremors resolved
  - Anxiety intermittent
- 6 months: HgA1c 6.4 → 5.2%

© 2016 Systems Biology Research Group

Questions and Comments

To learn more

- info@endobiogeny.com
- www.endobiogeny.com
- www.learnendo.lt

© 2015 Systems Biology Research Group