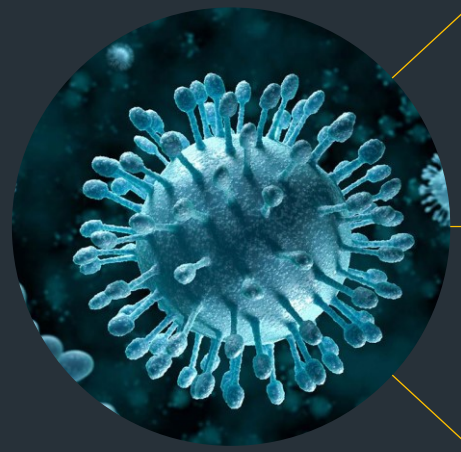
Heather Zwickey, PhD

Optimizing the Immune System in Chronic Infections

AARM
Association for the Advancement of Restorative Medicine

Ideal Responses to Infection



Th1

- Bacteria & Virus

Th17

- Mold & extracellular bacteria

Th2

- Some viral infections

Environmental Effects

Response to Infection

# of microbes

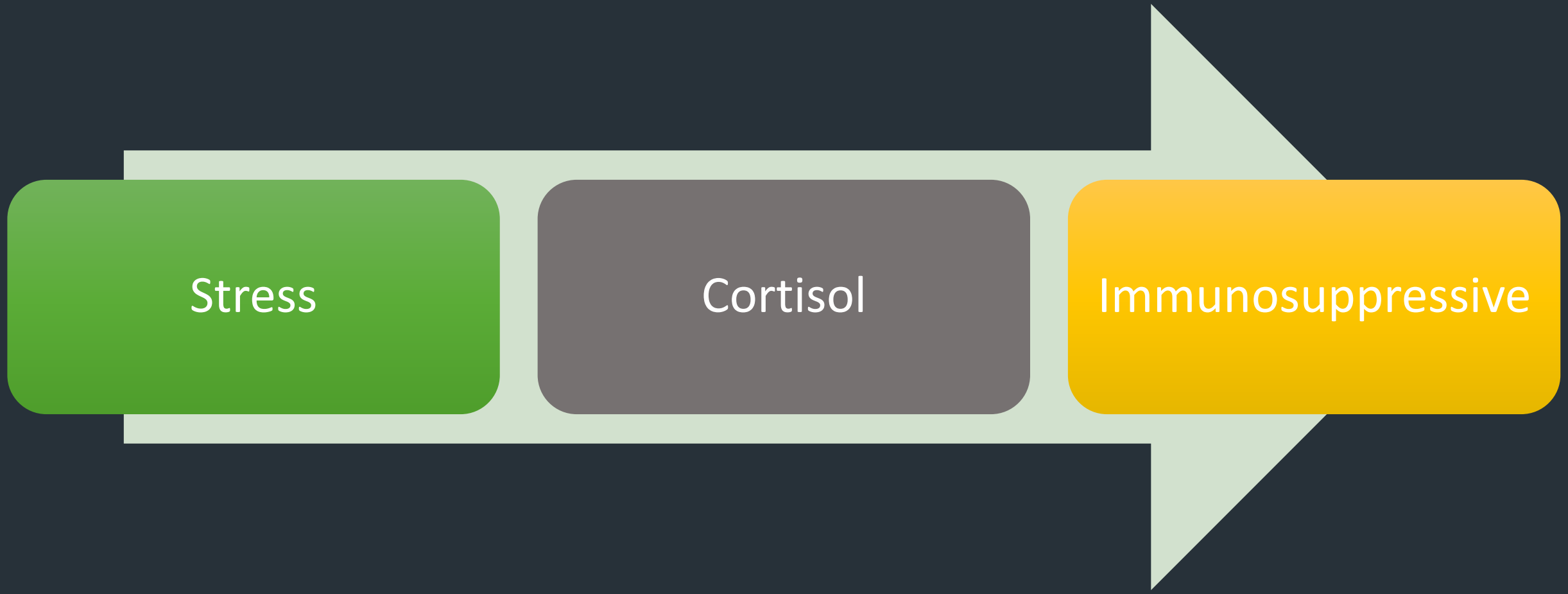
Virulence

Stress

Immune balance

“Health”

Historically…



Now… More complex than that.

Immune Balance

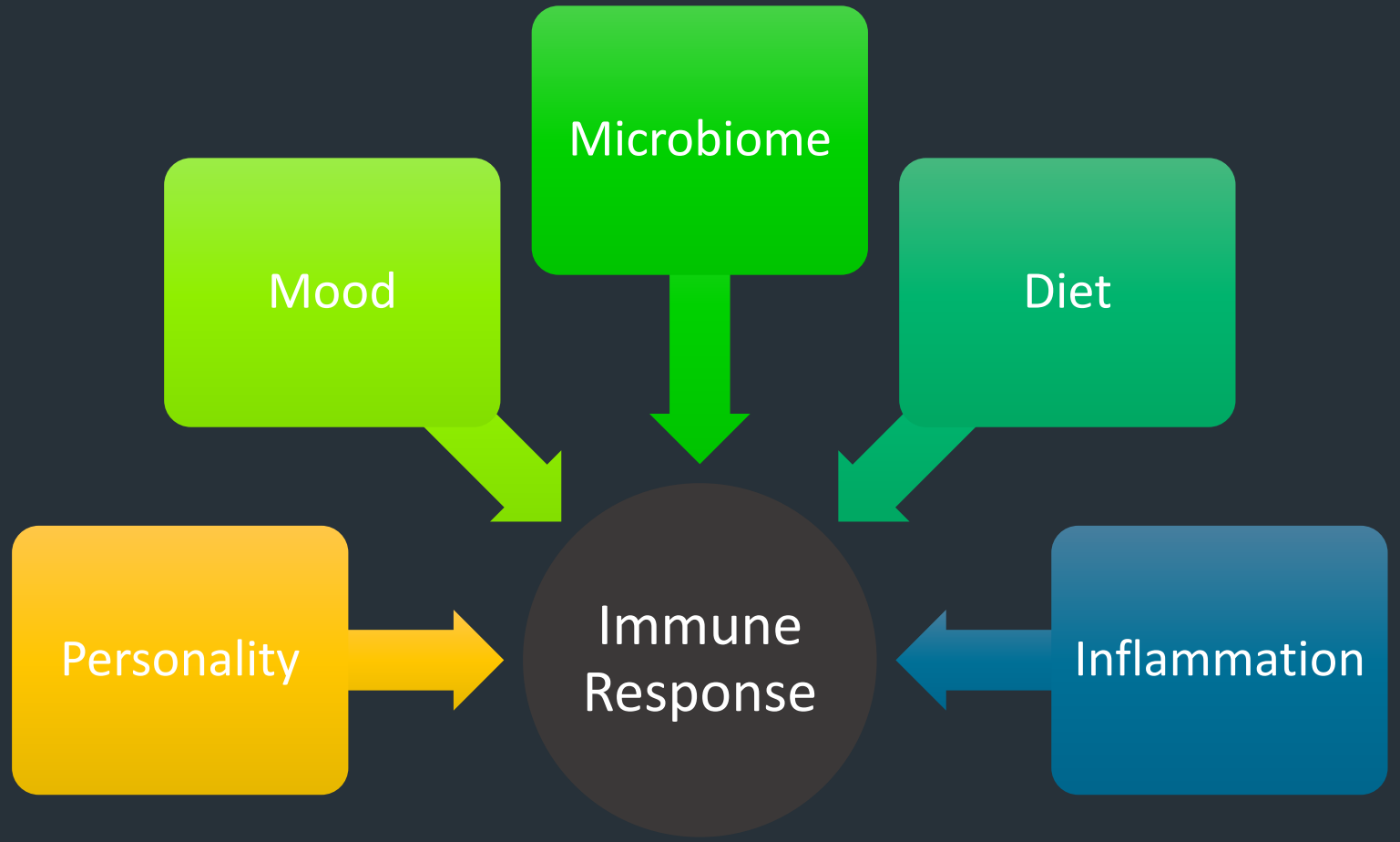
Th1

Able to quickly fight off infection

Th2

Seem to get many infections

“Health” impacts on infection



Objectives

After this lecture, you should be able to:

- Revisit the immune response to stress during infection
- Approach Th1/Th2 balance in chronic infection
- Discuss Gut/Brain Axis in chronic infection

Well-studied Moods

Stress

Bereavement

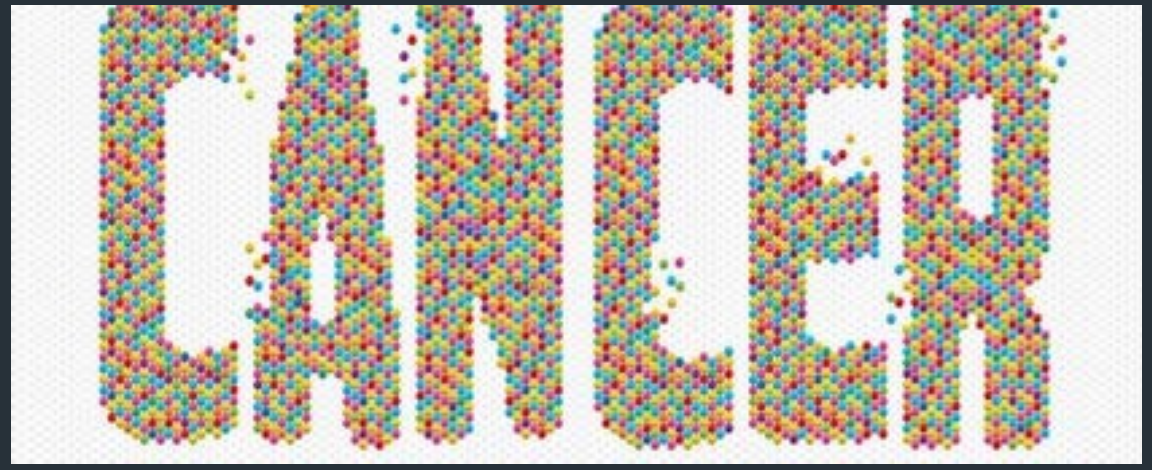
Happiness

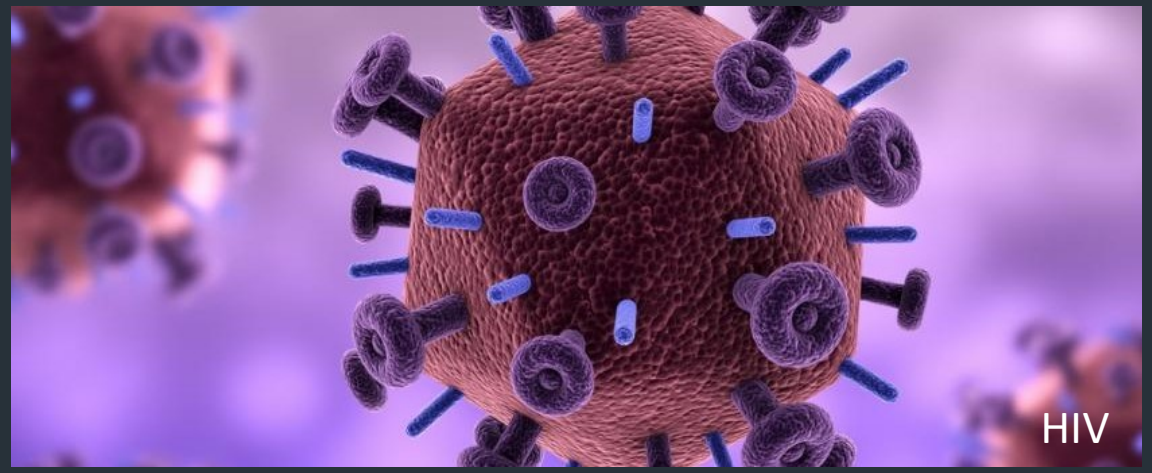
Stress

Why do we know so much about stress?

Bereavement

Why do we know so much about bereavement?





Happiness

Why do we know anything about happiness?

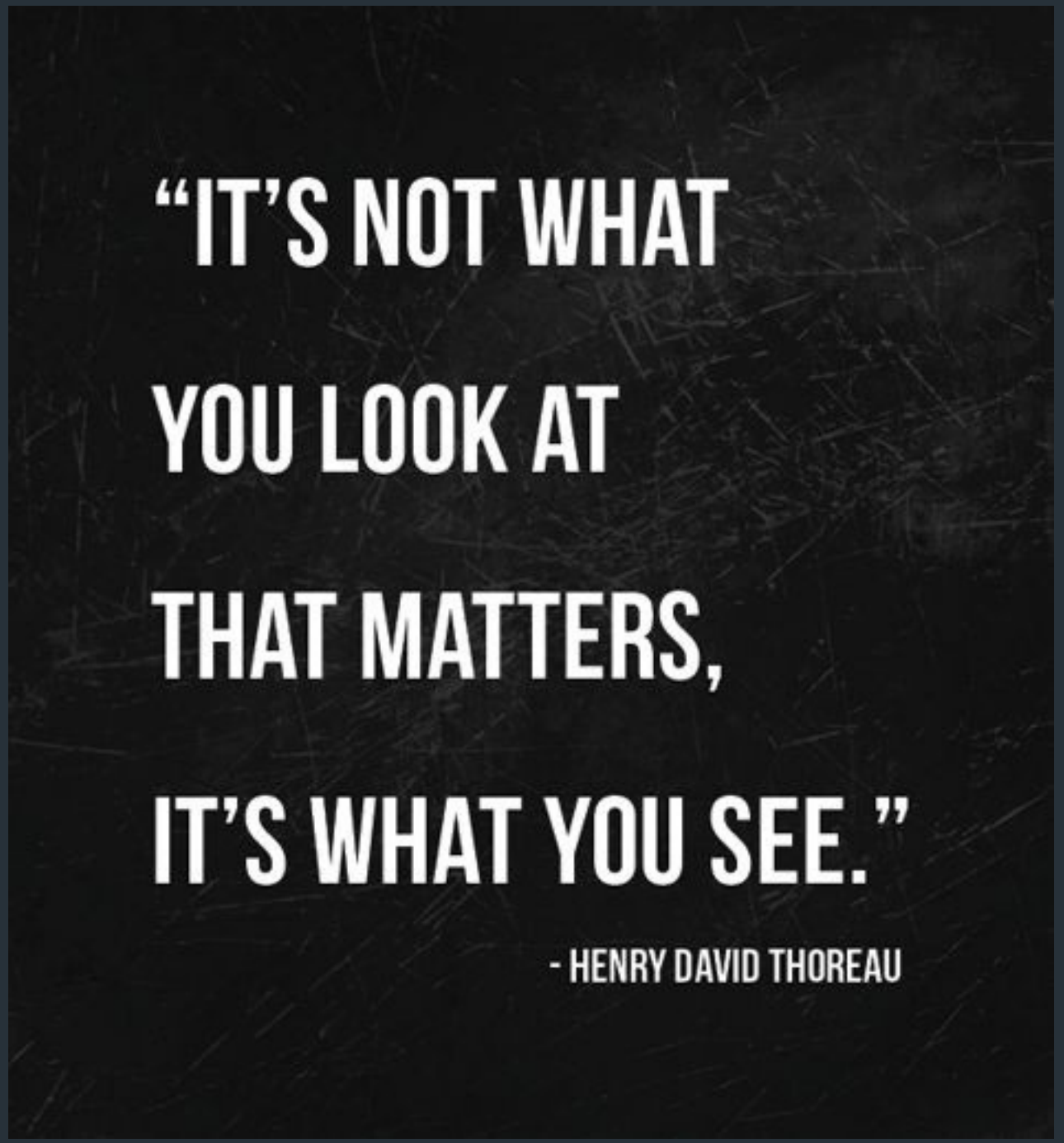
Stress – What is it?

Stress: the perception of threat to the physiological or psychological well being

and

the perception that the individual's responses are inadequate to cope with it.

★ **Abililty to Cope** ★

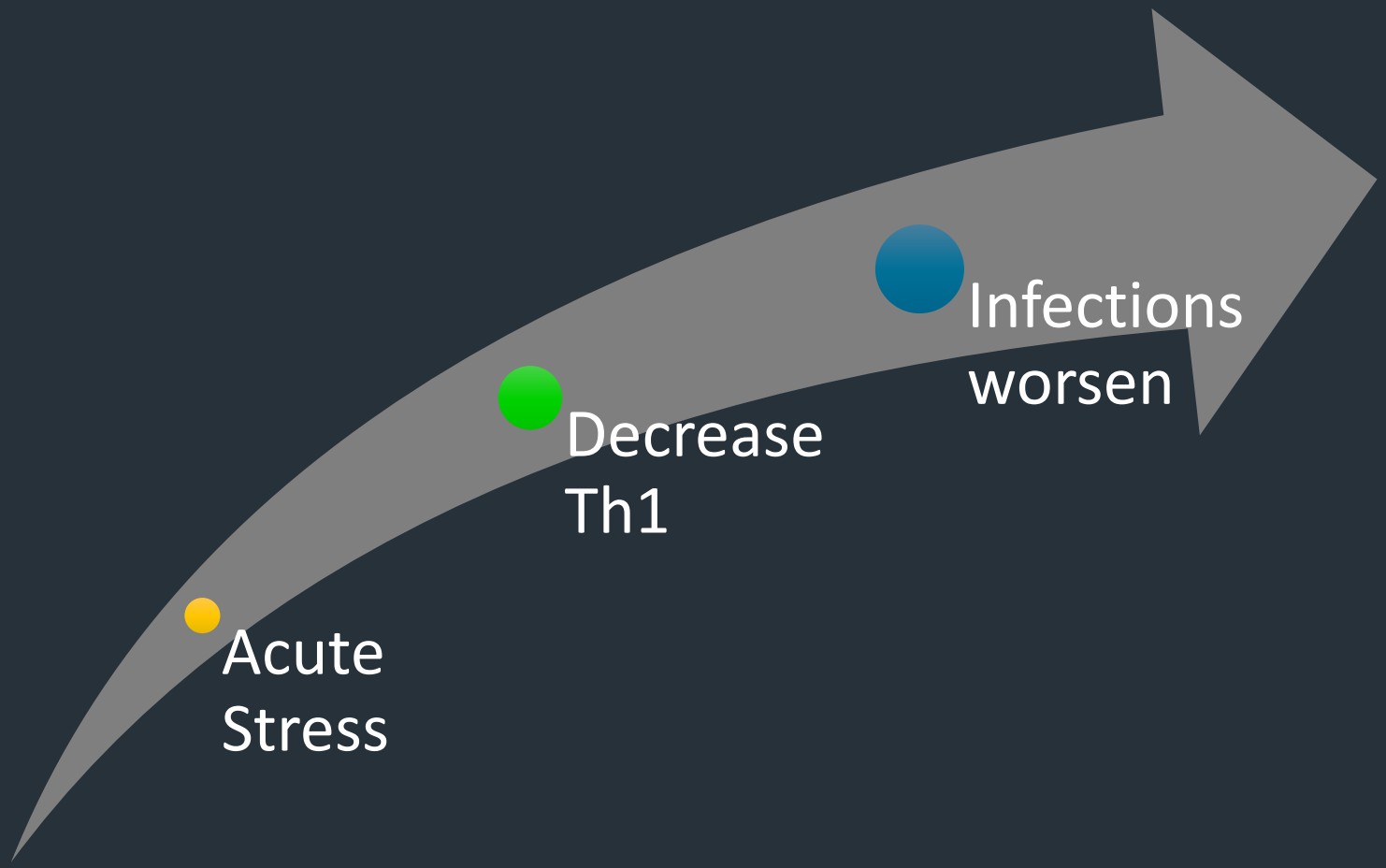

“IT’S NOT WHAT
YOU LOOK AT
THAT MATTERS,
IT’S WHAT YOU SEE.”
- HENRY DAVID THOREAU

Studies with medical students

- Exams and social support effect the response to Hepatitis vaccine response

- Isolate peripheral blood leukocytes
  - Treat with catecholamines
  - Shuts down IL-12 production
  - Reduces Th1 which increases Th2
  - Th2 is “allergy”

Implications for chronic infection

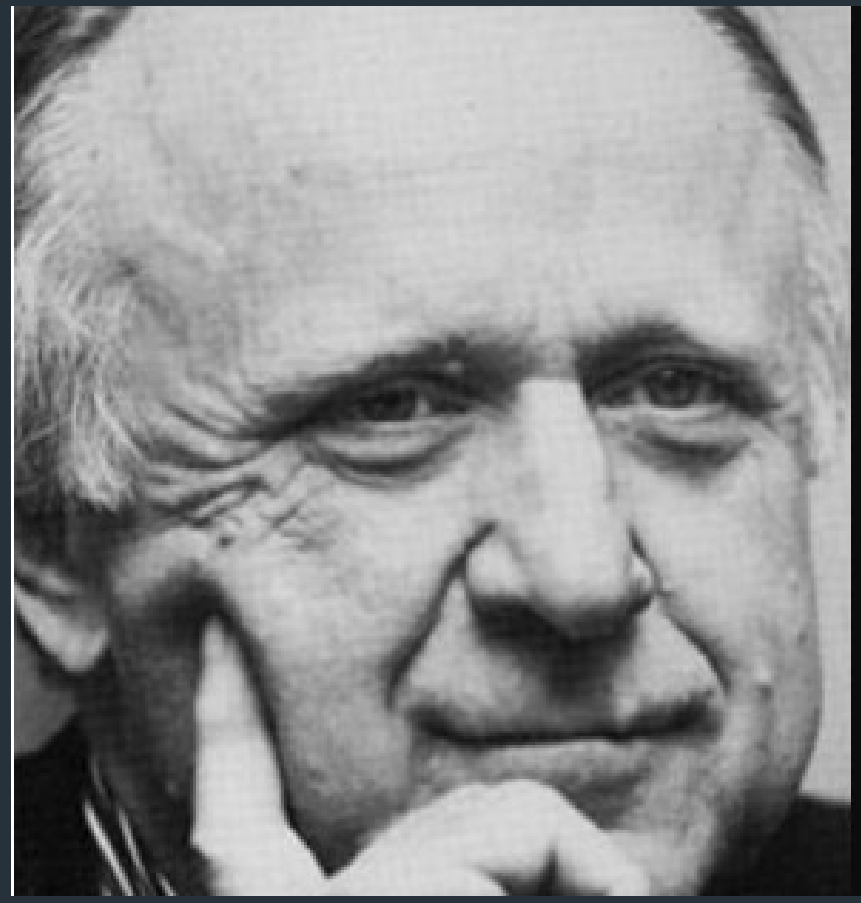


Other ways we study stress

Hostile marriage increases IL-6 and hs CRP

Rugby increase of IL-1b and TNFalpha

Why?



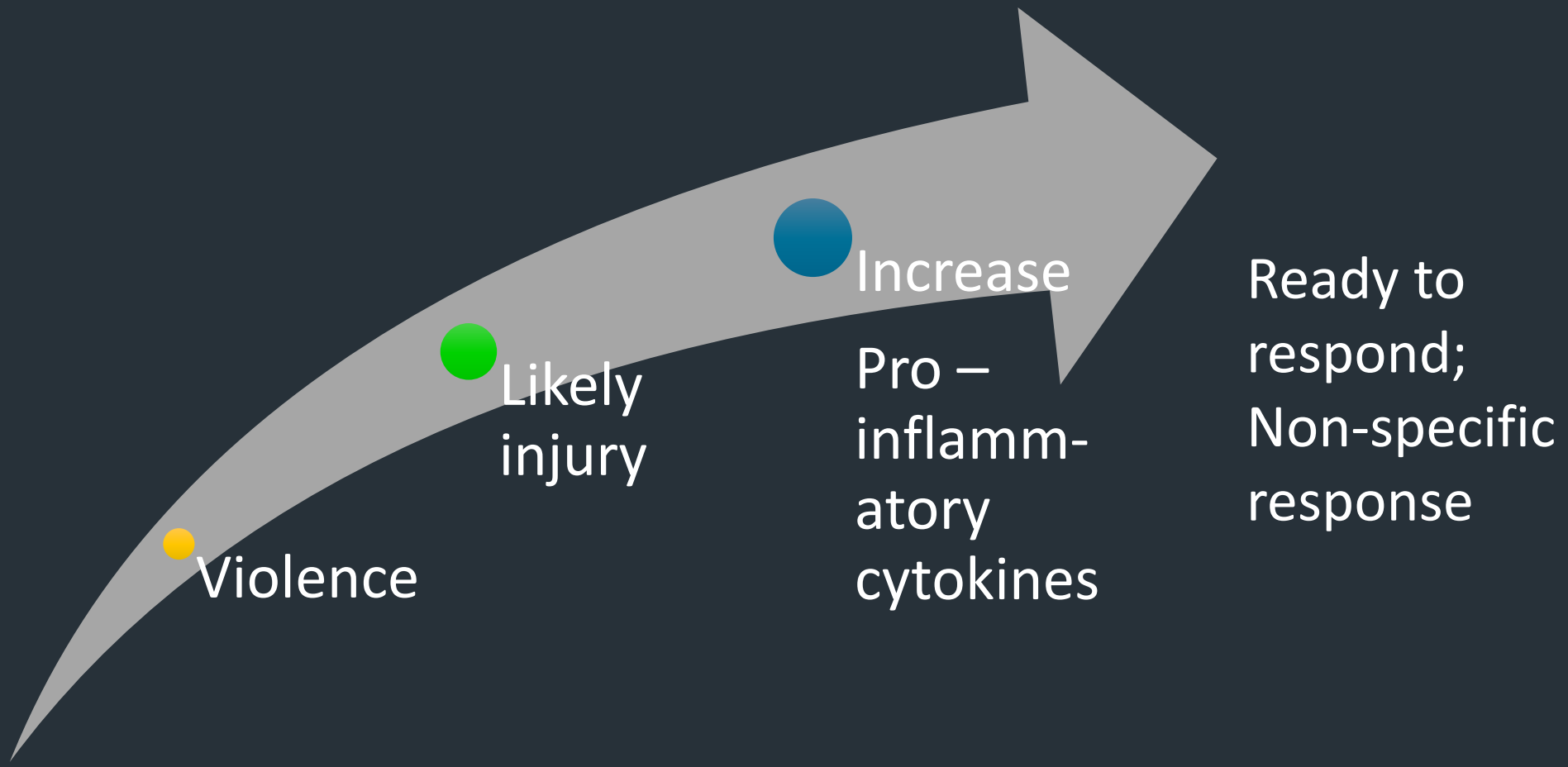
There is no escape - we pay for the violence of our ancestors.

— Frank Herbert —

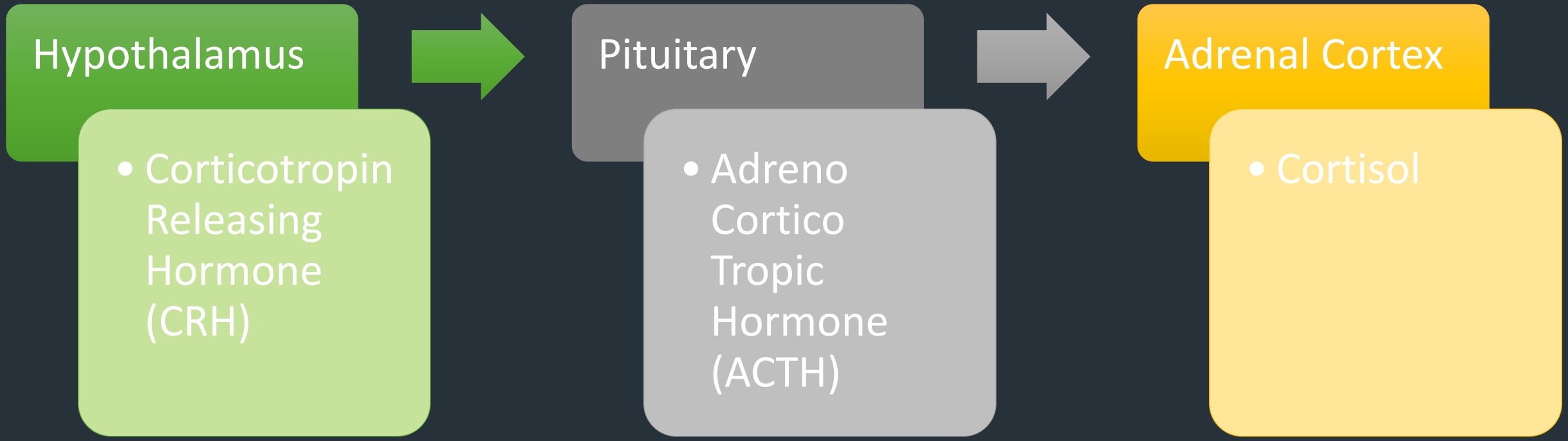
Ancestors

Persistent anger leads to longer wound healing time.

Implications



Stress Response Review



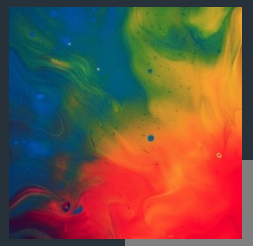
High Cortisol Effects (Acute Stress)

Endocrine

- Increases blood glucose
- Decreases testosterone

Immune

- Blocks T cell proliferation
- Reduce secretion of cytokines



Nervous

- Solidifies a memory
- Decreases overall memory over time

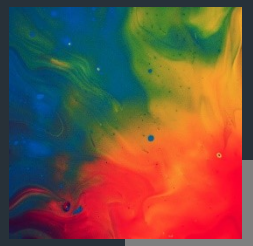
Chronic High Cortisol

Endocrine

- Decreased thyroid function
- Accumulation of abdominal fat

Immune

- Prolonged healing time
- Inability to respond to infections



Nervous

- Impaired cognition

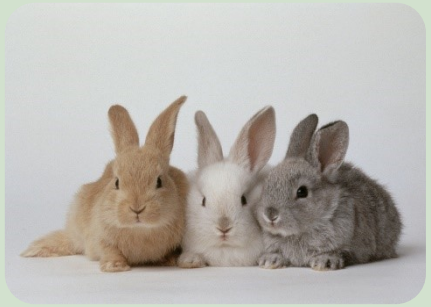
Inability to Respond to Infection

Chronic Stress

- Decrease in specific immunity
- BUT, increase in pro-inflammatory cytokines
  - IL-1, IL-6, TNF

- IL-6 – higher in women; More catastrophizing
  - IL-6 triggers CRP production
  - Chronic stress = chronic inflammation

Effects of Hormones on the Immune System



Cytokines

Cell Trafficking

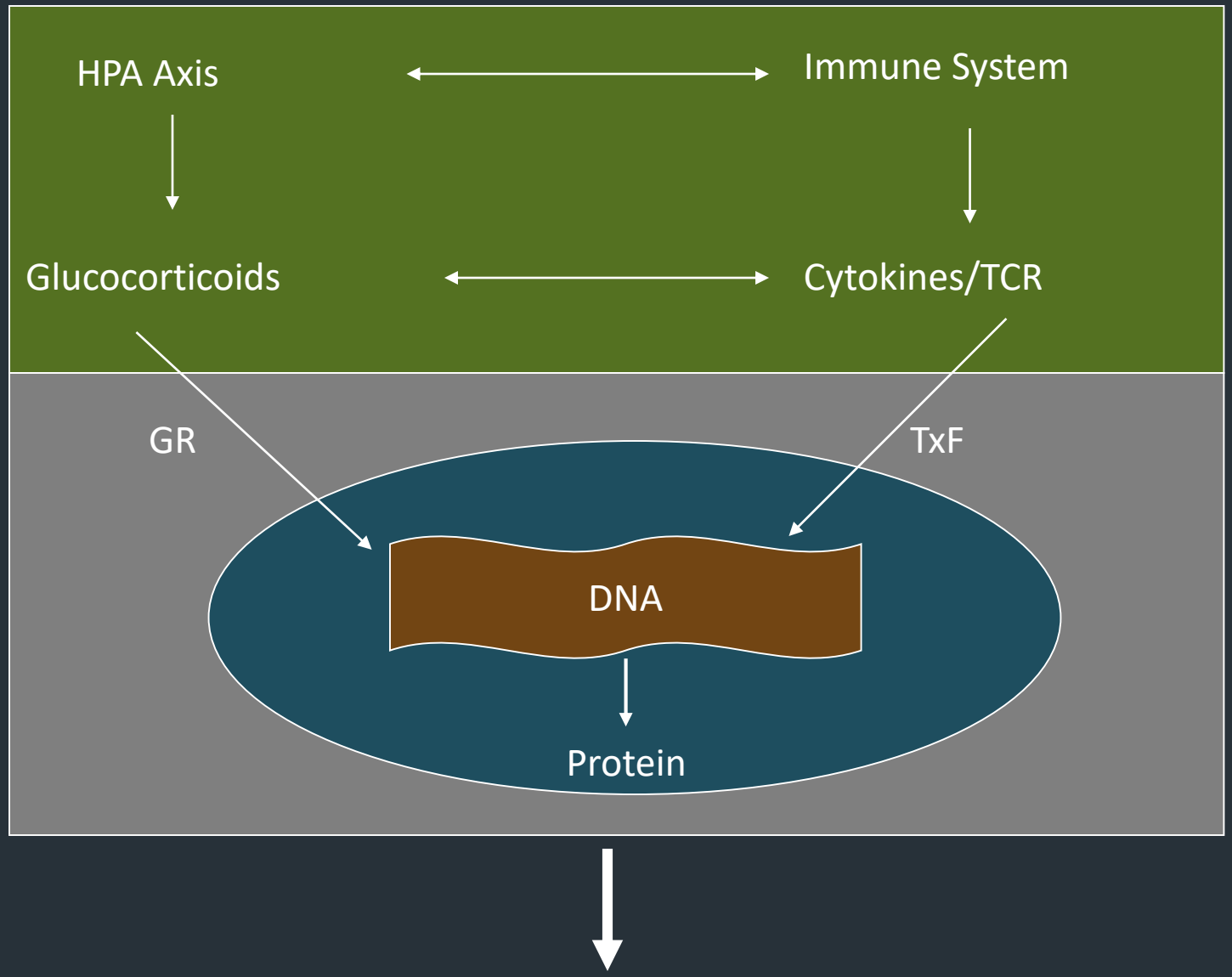
Adhesion Molecules

Proliferation

Effector Functions

Systemic

Cellular and Molecular



Biological Response

Adapted from Arzt et al. 2001

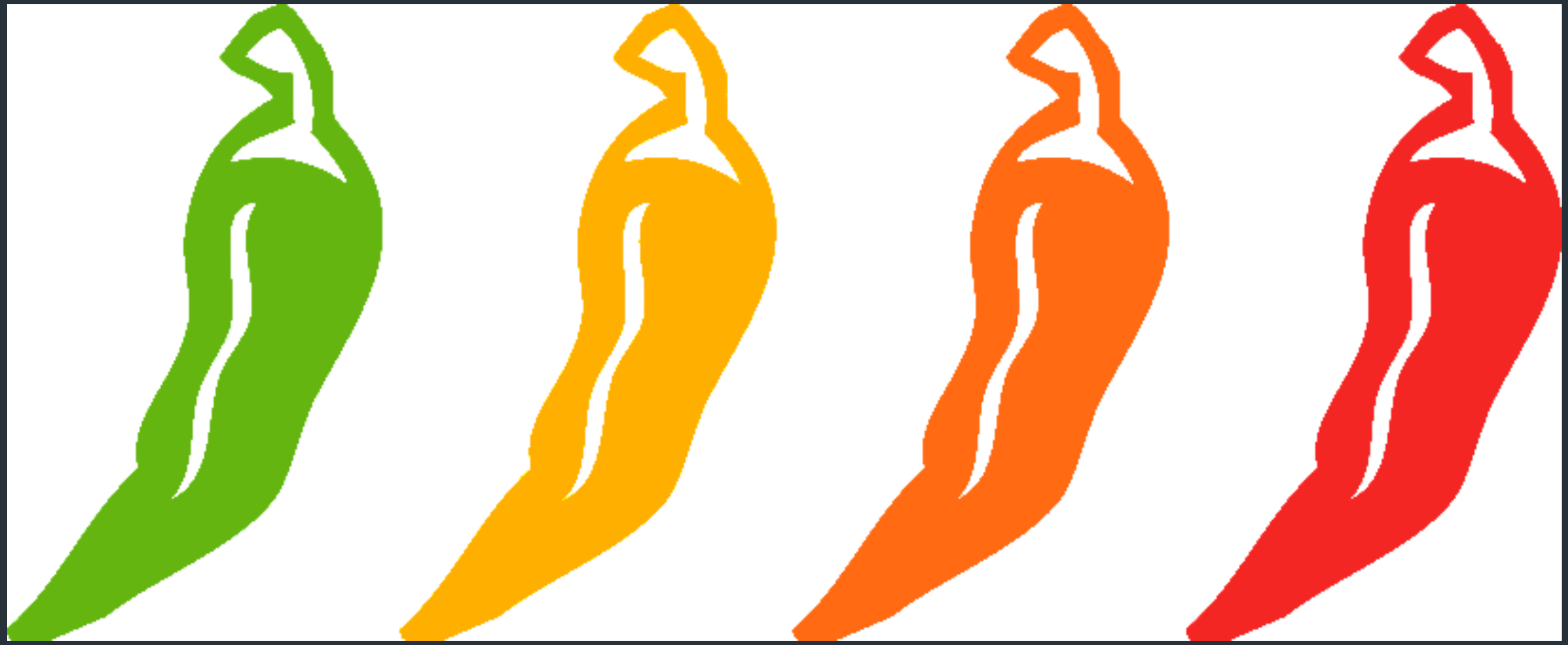
Glucocorticoid Mechanism of Action

- Glucocorticoid receptors are transcription factors
  - Cytokine genes have Glucocorticoid Response Elements
  - Glucocorticoids can regulate how much cytokine is made

Hormones and Cytokines

Hormone	Endocrine Activity	Immune Effect
Testosterone	Sex steroid hormone	Decreases Th1 (increases Th2) Decreases pro-inflammatory cytokines
Estrogen	Sex steroid hormone	Increases Th1 & Th17 Increases antibody High in RA and SLE
Progesterone	Helps maintain pregnancy; Luteal phase	Shifts from Th1→Th2 Inhibits IL-6, TNF, IFNg Pre-eclampia = high Th1
Prolactin	Lactation; Sexual health in men and women	Increase Th1, Increases antibodies, may increase Th17 (autoimmunity)
Oxytocin	Bonding	Anti-inflammatory, Antibiotic, Wound Healing
DHEAS	Precursor for Testosterone and Estrogen	Decreases IL-6 and IL-12; Increases IL-10

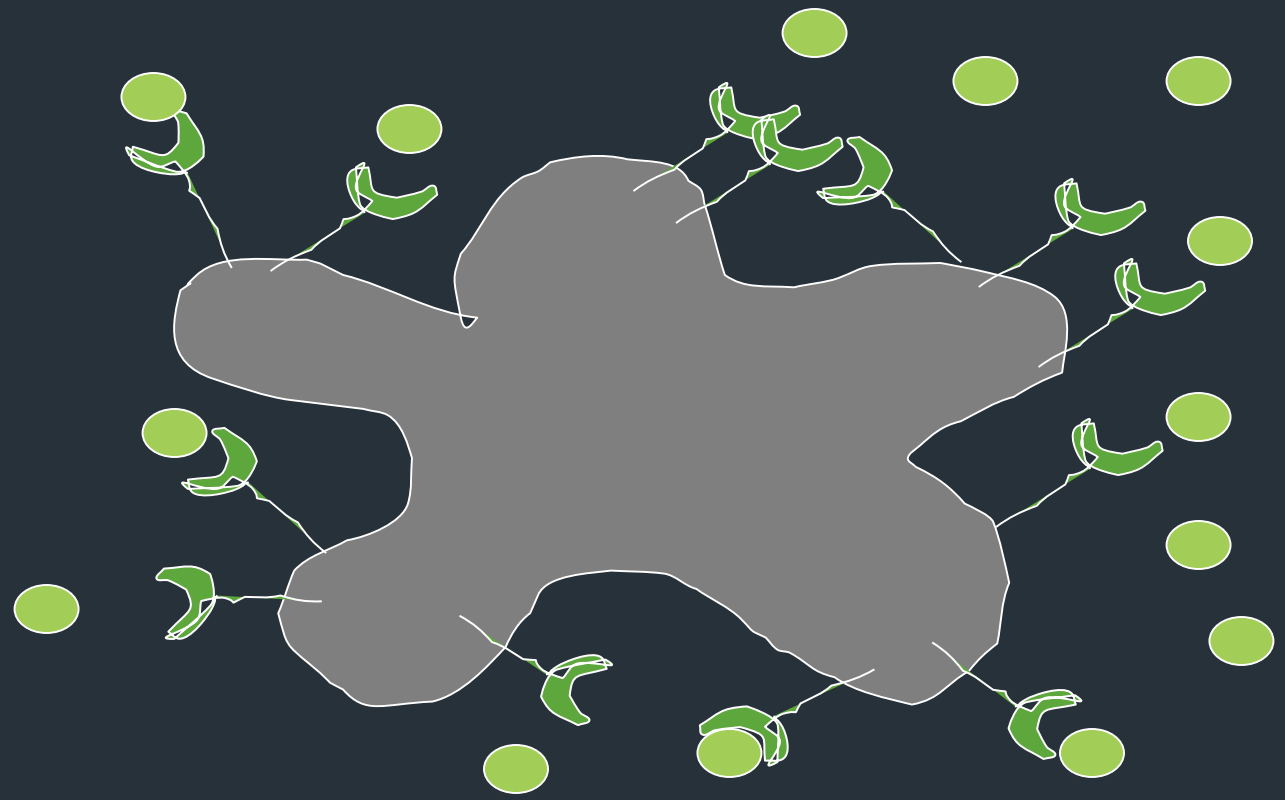
Level of Stress Matter (Mild vs Extreme)



Macrophages
Express both
α and β adrenergic
receptors

α receptors are high affinity-

Bind low concentrations of epi



β receptors are low affinity-

Bind high concentrations of epi

α receptors are high affinity-

Bind low concentrations of epi

Low Stress– bind α-receptor

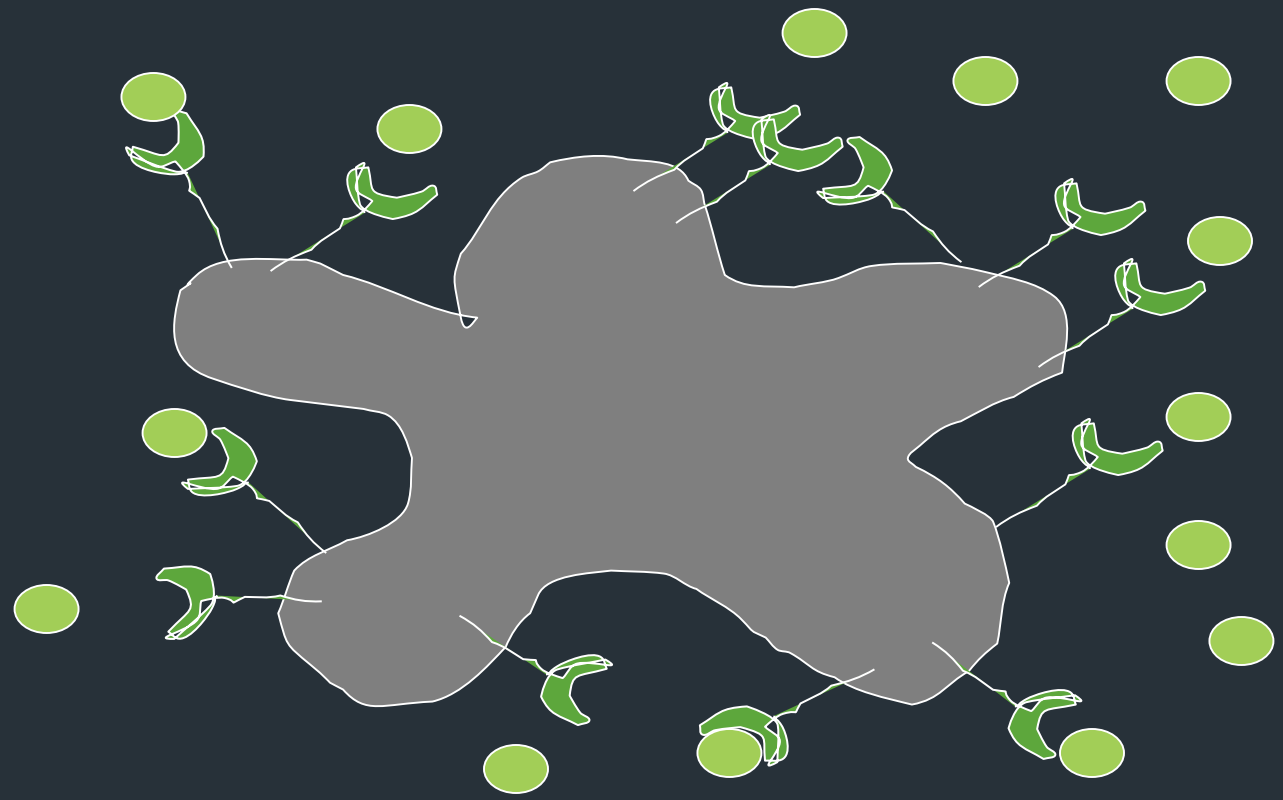
Results upon infection:

- **increases phagocytosis,**
- **increases TNFa**,
- **increases IL-6**

High Stress– bind β-receptor

Results upon infection:

- **decreases phagocytoisis,**
- **decreases antigen processing and presentation,**
- **decreases production of IL-12.**



β receptors are low affinity-

Bind high concentrations of epi

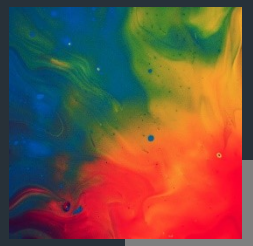
Catecholamine Effects (Adrenalin)

Endocrine

- Decreases prolactin
- Decreases testosterone
  - Studied in the military

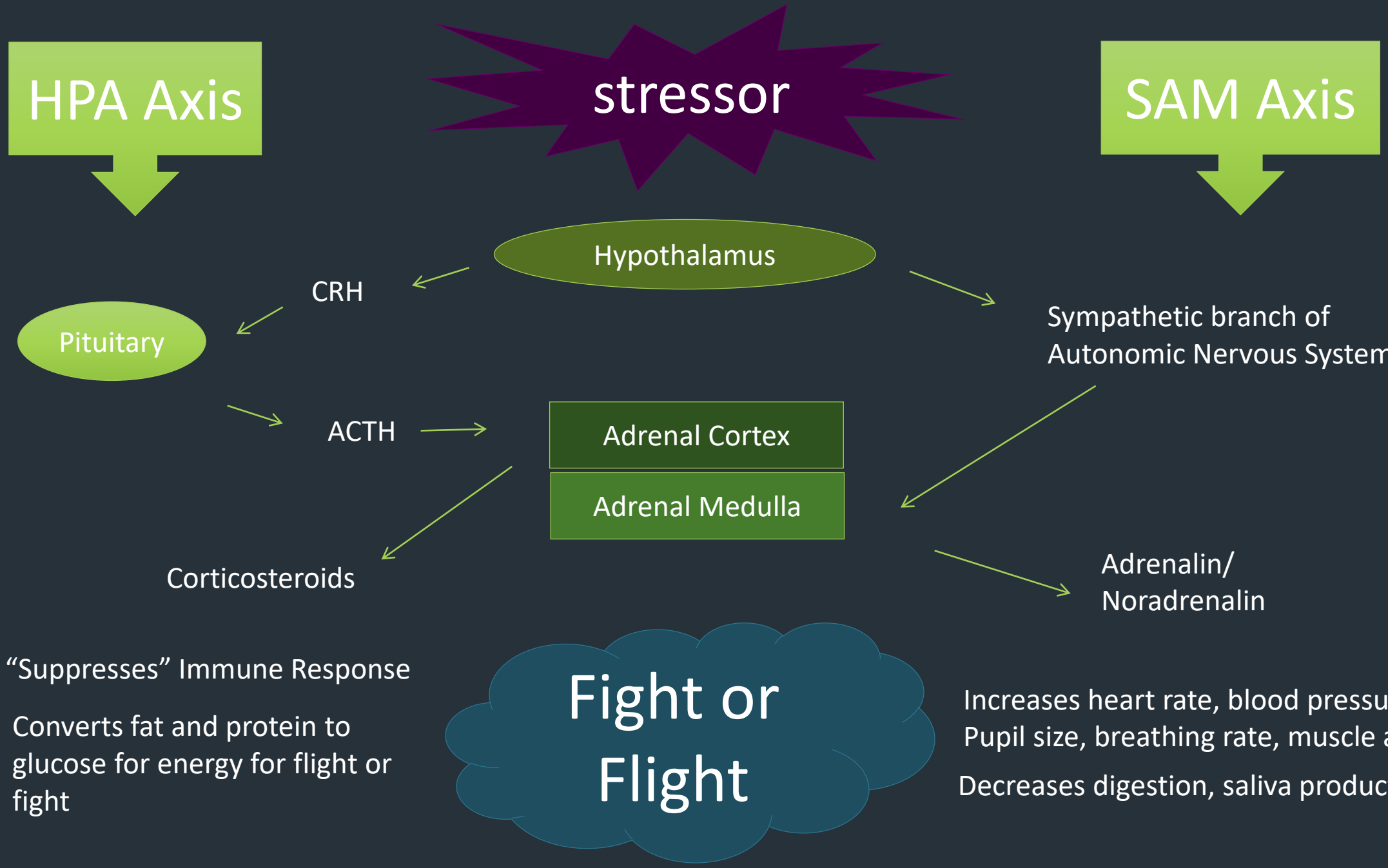
Immune

- Decrease Treg
- Increase Th1
- Decrease Th17
- Different than cortisol



Nervous

- Degrades memory in simulated interrogation
- Recovers faster than biomarker


HPA Axis
stressor
SAM Axis
Hypothalamus
CRH
Pituitary
Sympathetic branch of
Autonomic Nervous System
ACTH
Adrenal Cortex
Adrenal Medulla
Corticosteroids
Adrenalin/
Noradrenalin
"Suppresses" Immune Response
Converts fat and protein to glucose for energy for flight or fight
Fight or Flight
Increases heart rate, blood pressure, Pupil size, breathing rate, muscle activity
Decreases digestion, saliva production

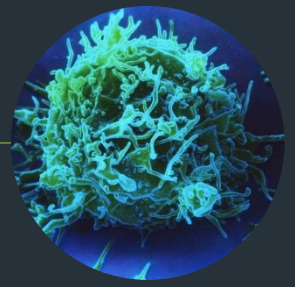
Advocating for vacations and siestas

It’s not stress that kills us, its our reaction to it.

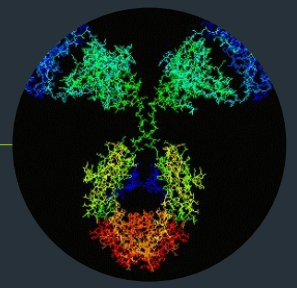
Does all of this reverse with relaxation?

- As adrenalin declines, people feel stable and comfortable, but maintain feelings of motivation
- Immune system recovers
  - Alpha adrenergic receptors engaged instead of beta

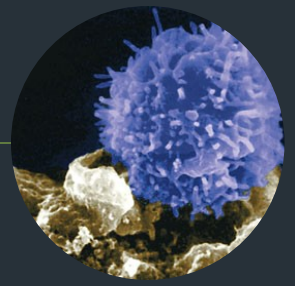
Laughter



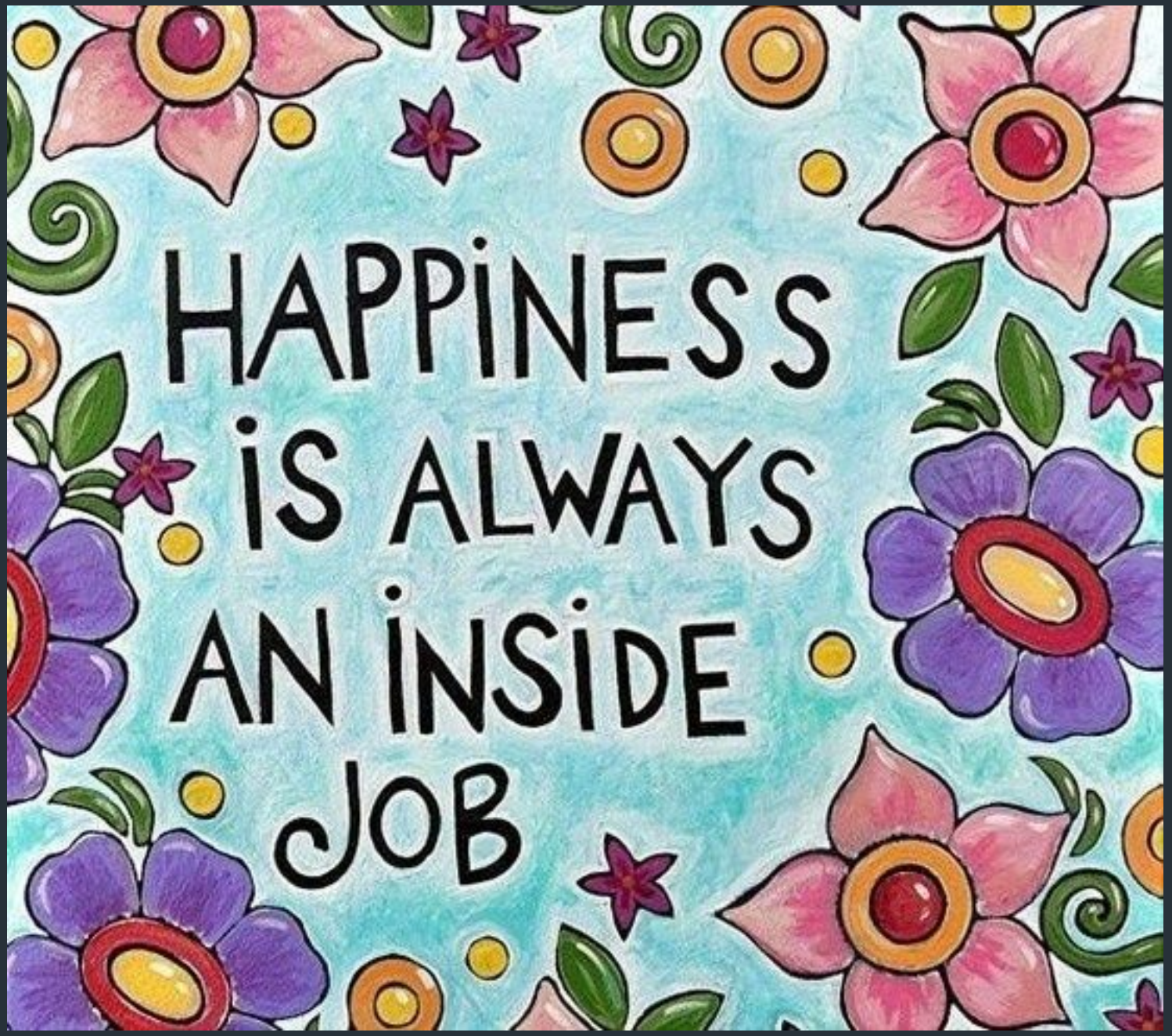
Increase
NKs



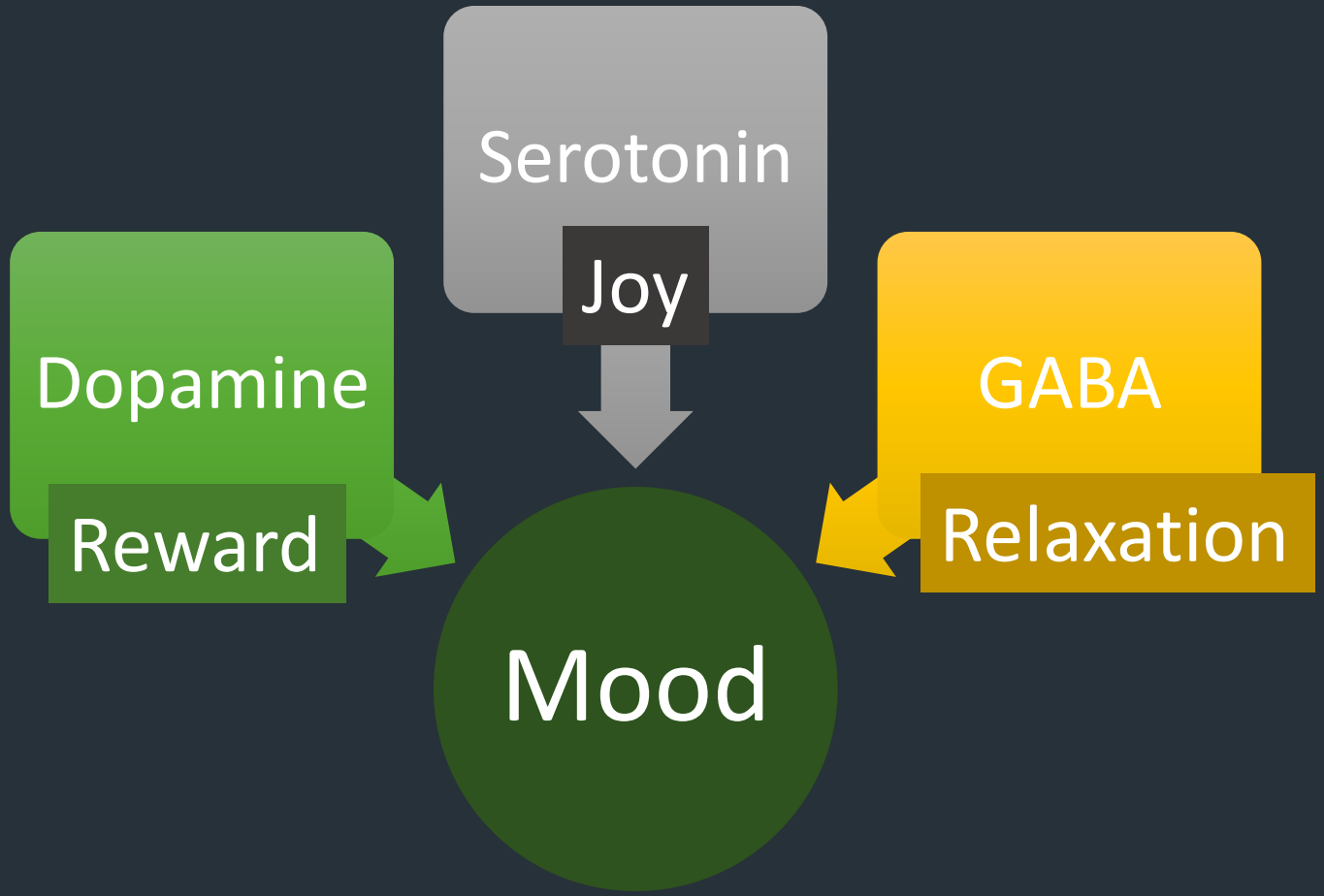
Increases
Antibodies



Decreases Pro-
inflammatory
Cytokines


HAPPINESS
IS ALWAYS
AN INSIDE
JOB

Neurotransmitters and Microbiome



Neurotransmitter Summary

Neurotransmitter	Mood Effect	Gut Effect	Immune Effect
Dopamine	Pleasure/ Depression	Colon contraction	Drives Th17 or Treg depending on level
Serotonin	Happy/Anxiety	Bowel movements	Serotonin and IFNgamma compete for tryptophan
GABA	Relaxation/ Depression/Mania	Intestinal motility; Pain reduction	Decrease inflammatory cytokines

Cell	Express Receptors:
CD4 T cell	β adrenergic receptor Dopamine receptor Acetylcholine receptor 5HT receptor Opioid receptor (?)
CD8 T cell	Dopamine receptor 5HT receptor
B cell	Dopamine receptor
NK cell	Dopmine receptor Opioid receptor
Macrophage	Dopamine receptor α and β adrenergic receptor
Dendritic cell	Dopamine receptor Opioid receptor

Effects of Endorphins on Immunity

- Opioid abusers have higher incidence of infections
  - Impaired immunity
- Opioid treatment results in reactivation of latent viruses
  - *If you're placing a patient on opioids, consider this*
  - Slows clearance
  - Increases risk of secondary infections

- Influenza
  - Morphine impairs immunity in lungs
  - Opioids decrease NK cell activity
  - Opioids increase risk of pneumonia

Alireza Tahamtan,1 Masoumeh Tavakoli-Yaraki,2 Talat Mokhtari-Azad,1 Majid Teymoori-Rad,1 Louis Bont,3 Fazel Shokri,4 and Vahid Salimi1, "Opioids and Viral Infections: A Double-Edged Sword" Front Microbiol. 2016; 7: 970.*

Endocannabinoids

- Endogenous set of neurochemicals
  - Discovered through effects of Cannabis sativa
  - CB1R is expressed in the brain and peripheral tissues
    - Associated with cognition and movement
  - CB2R is on lymphoid cells
    - B, T, Mac, DC, Neuts, and NKs
    - Involved in psychiatric disorders including schizophrenia, depression, and bipolar disorder

Effects of Endocannabinoids on Immunity

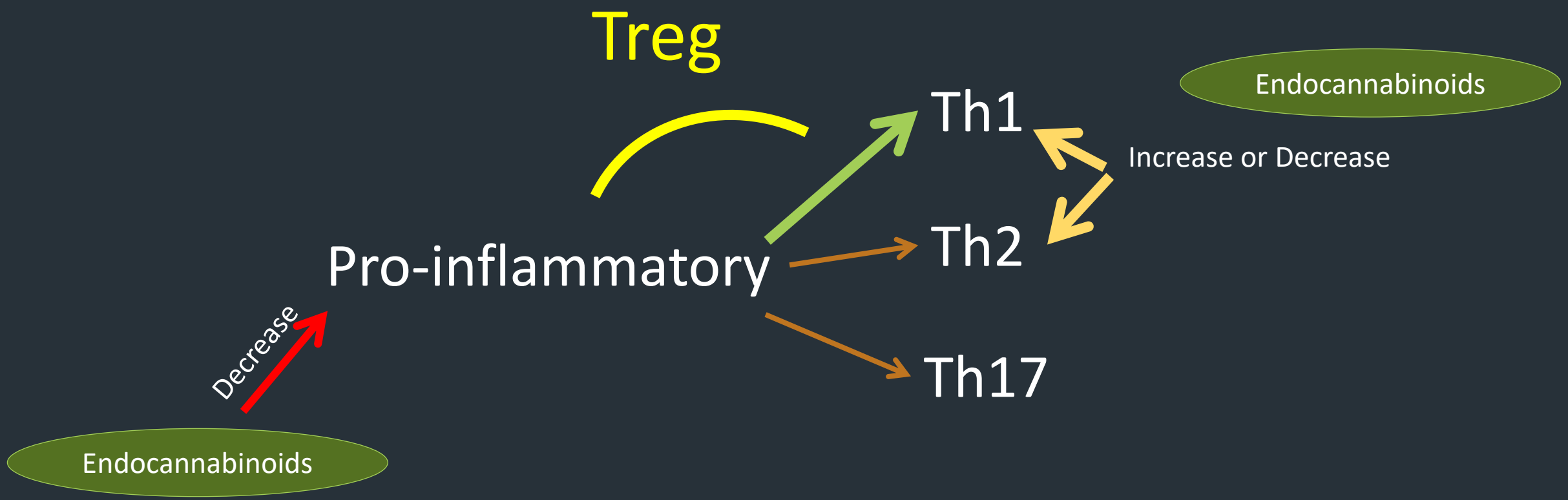
Pathogens stimulate macrophages and DCs

Reduce expression of endocannabinoid-degrading enzymes

Increases endocannabinoids in the body

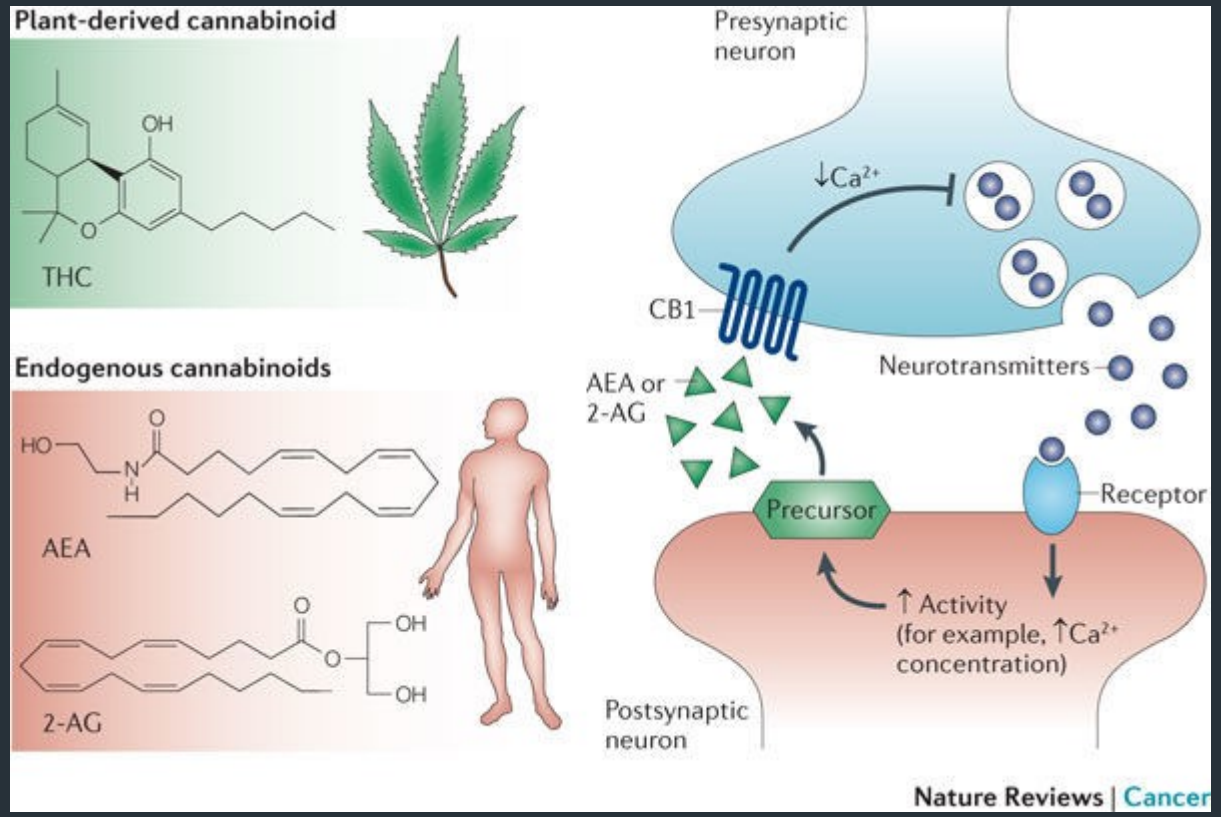
Increases B cell migration; Shifts cytokine profiles

Endocannabinoids and Immunity



Rupal Pandey, Khalida Mousawy, Mitzi Nagarkatti, and Prakash Nagarkatti. Endocannabinoids and immune regulation. Pharmacol Res. 2009 Aug; 60(2): 85–92.

Endocannabinoids ≠ Cannabis



Endo

- Endocannabinoids modulate Th1 and Th2

Plant

- Plant derived cannabinoids increase Th2

Stimulating Endocannabinoids without Cannabis

Polar plunge!

Magnolia

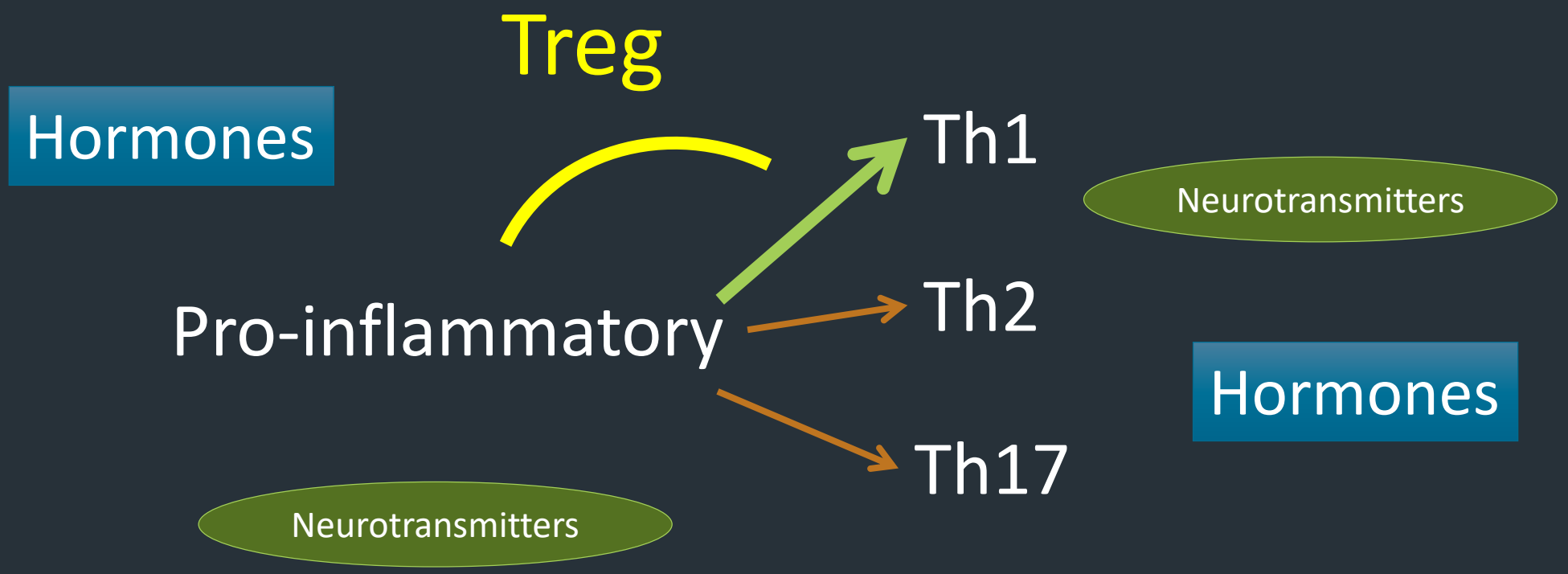
Caffeine

Olive Oil

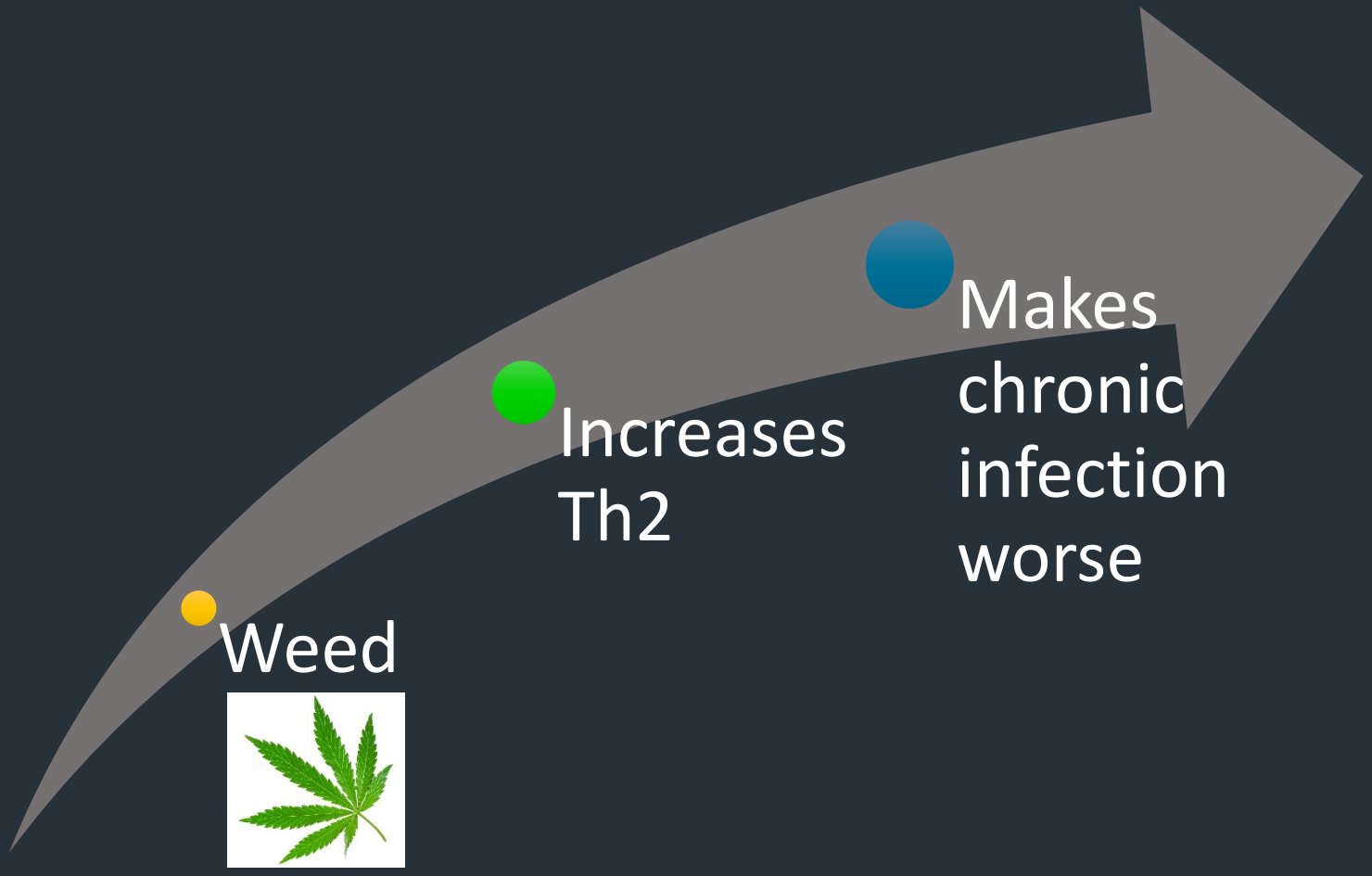
Kava

Flavonoids

Balance

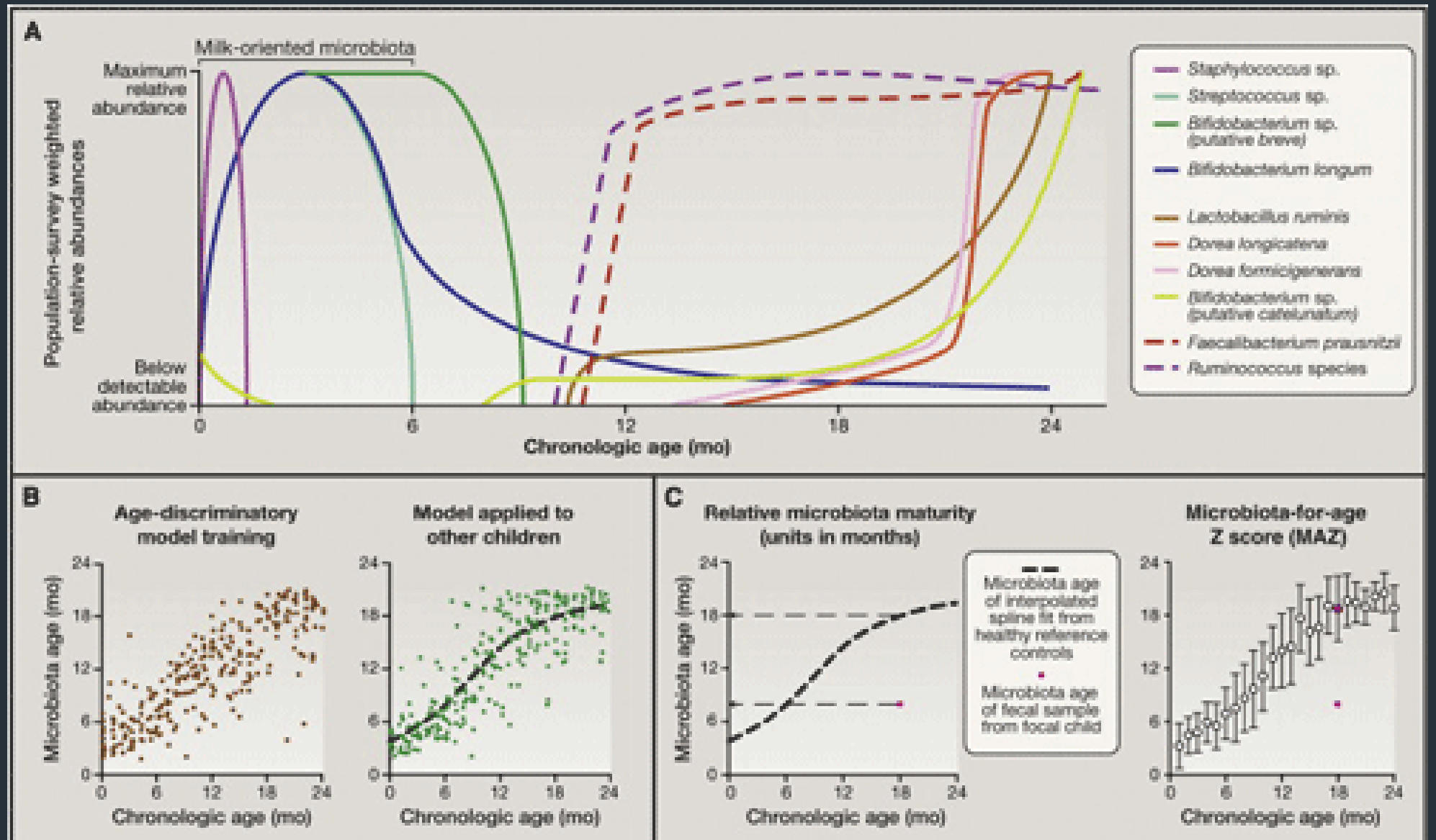

Treg
Hormones
Th1
Neurotransmitters
Pro-inflammatory
Th2
Hormones
Th17
Neurotransmitters

Implications

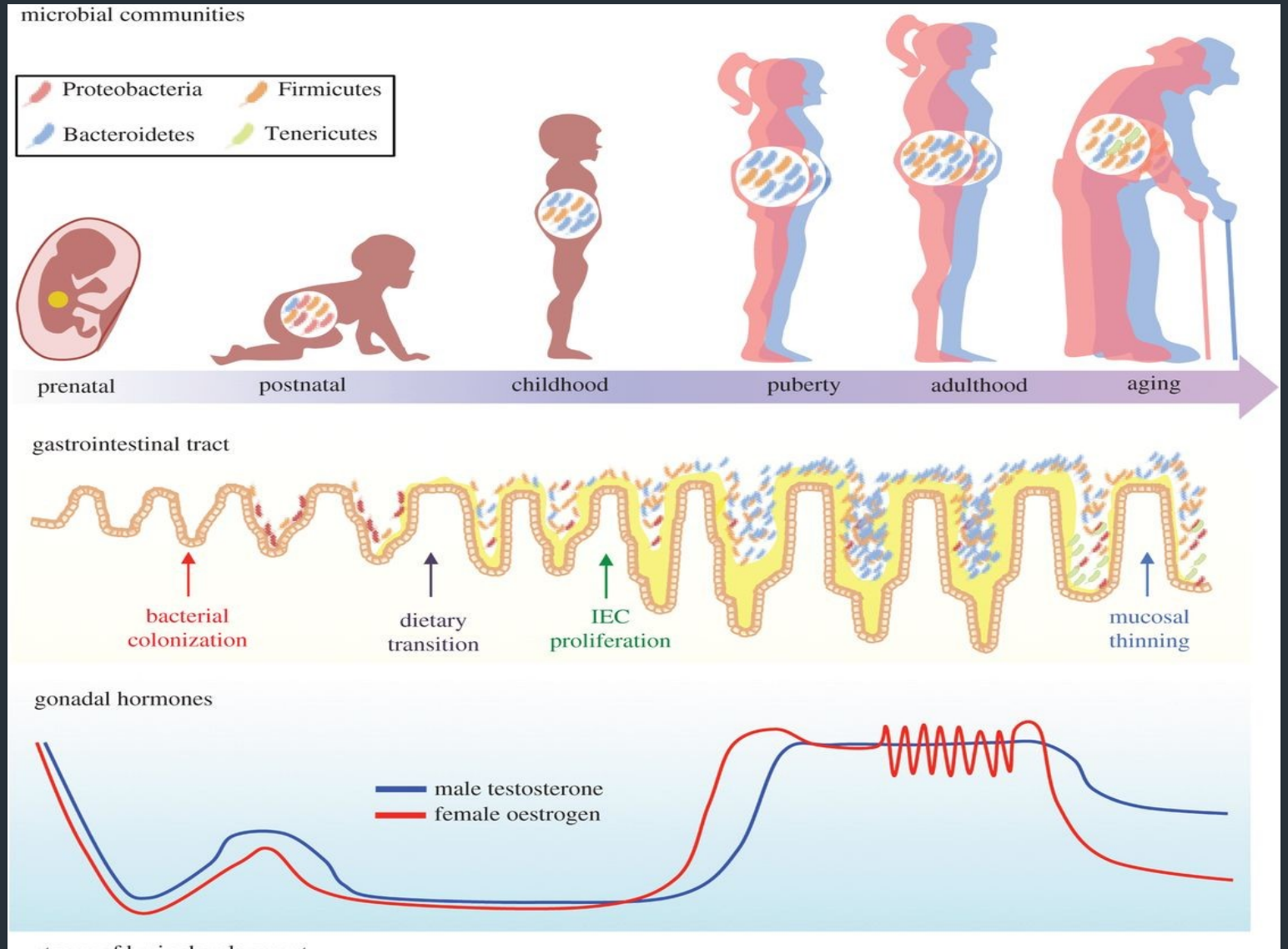


Diet & Microbiome

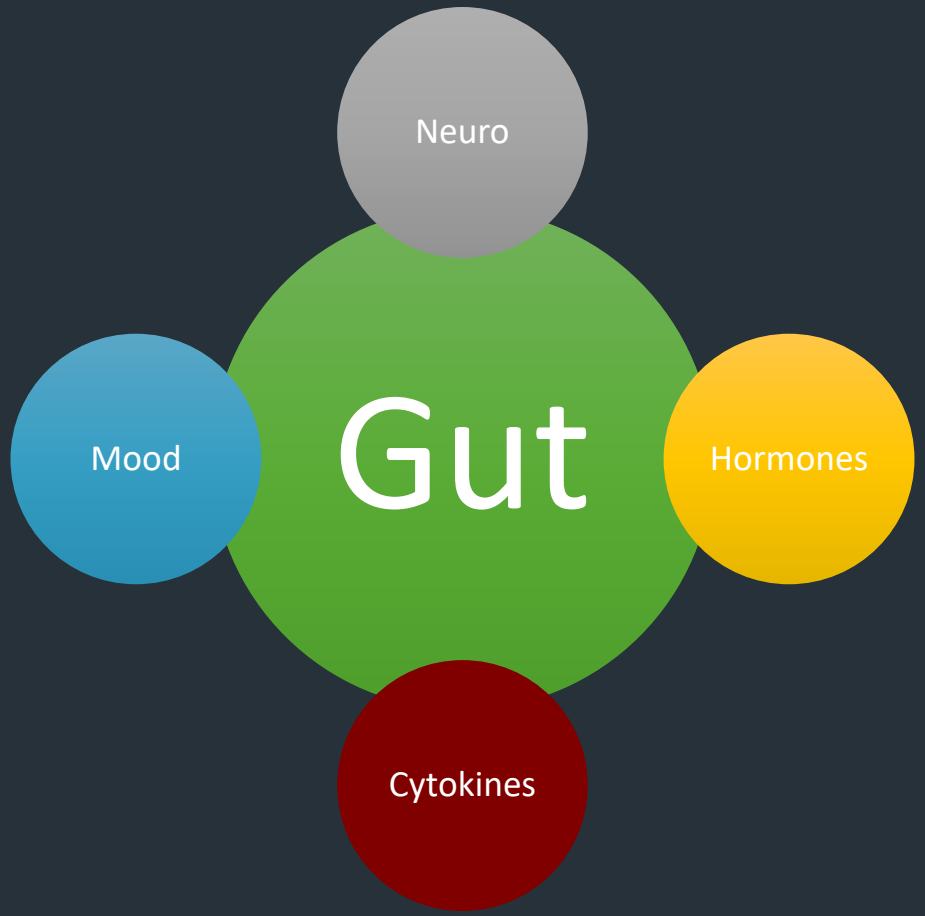
Microbiome Development



Immune development follows microbiome development



It’s all connected…



- Gut is huge source of neurotransmitters and cytokines
- Microflora produce neurotransmitters (Dopamine, Serotonin, and GABA) and influence production of neurotransmitters
- Microflora can impact immune outcomes

Diversity Between People

No 2 people have the same microbiome

However, several microbe species can induce the same gene functions

Several microbe species have the same metabolic function

Microbiome can impact inflammation

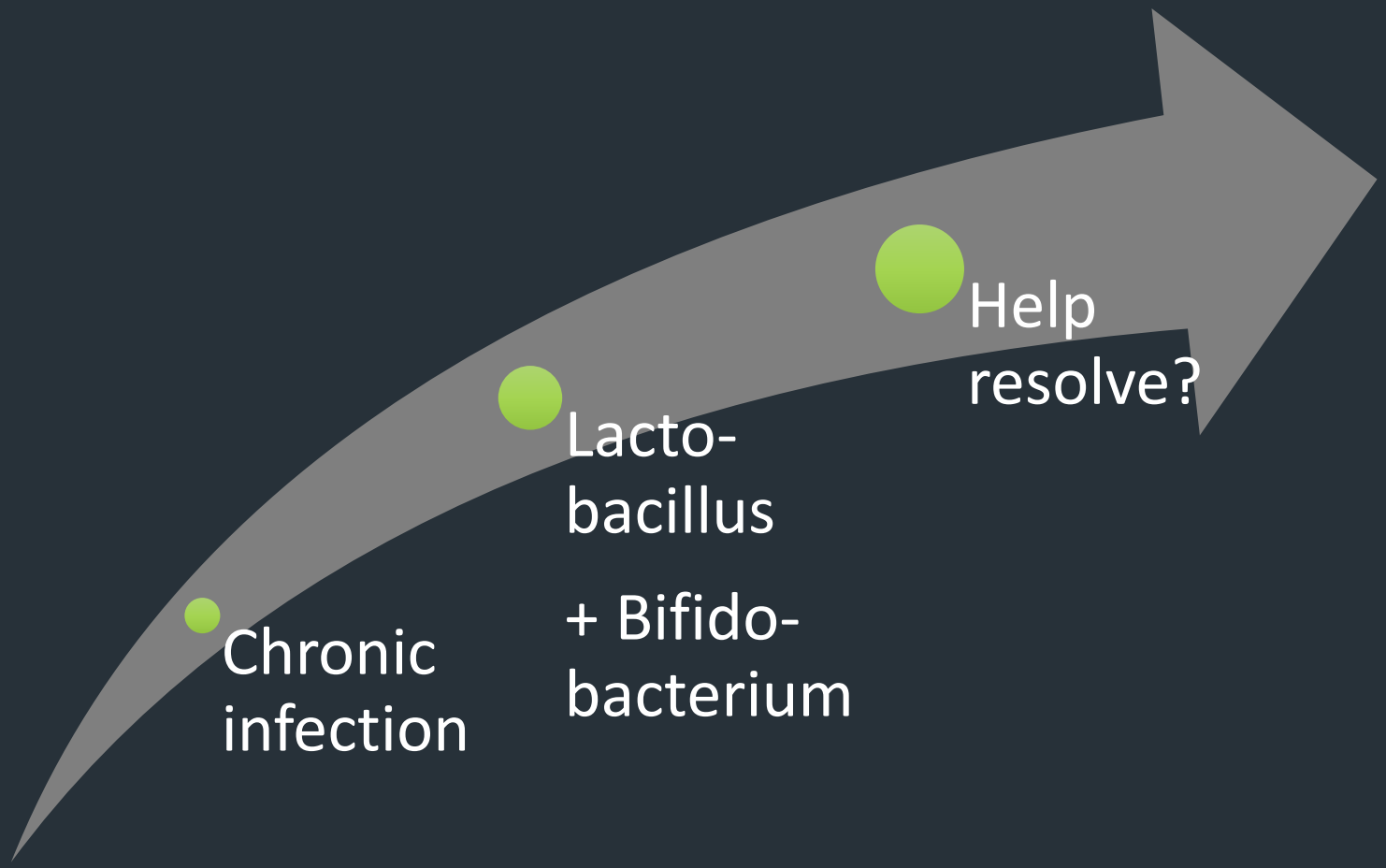
Lactobacillus

- Th1 or Treg

Bifidobacterium

- Treg

Implications



Adding level of complexity

Bacteroides + Vegetarian Diet = Treg

Bacteroides + Meat Diet = Th1

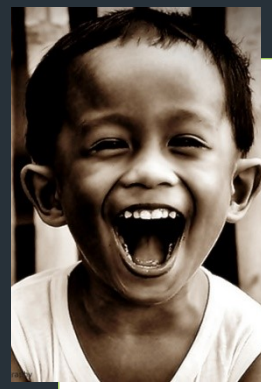
Summary

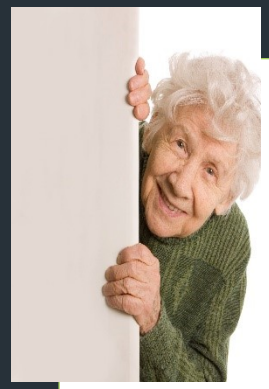
Chronic infection is negatively impacted by stress

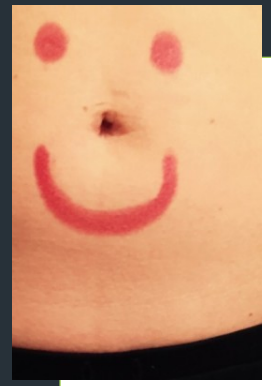
Clinicians should choose therapies that drive Th1 or Th17 to resolve infection

Things that drive Th2 (allergies, weed) can make infection worse

Summary







Thank you!!!

Thanks to

Association for the Advancement of Restorative Medicine

NIH National Center for Complementary and Integrative Health

Zamia

Nutrition by Heather Zwickey