How Evolution Encourages Good Questions about Cancer

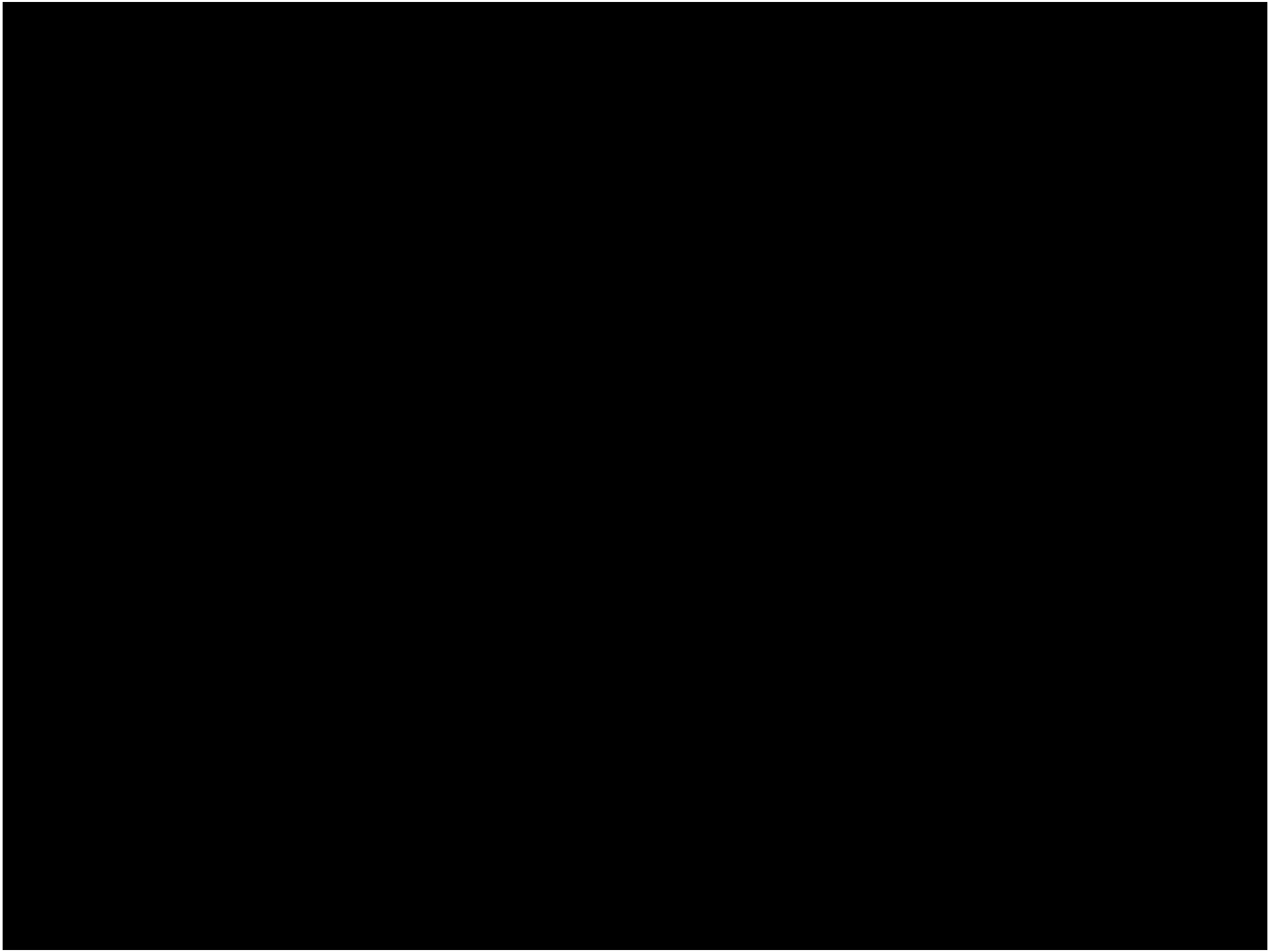
Randolph M. Nesse, M.D.
The University of Michigan

War on Cancer at 40

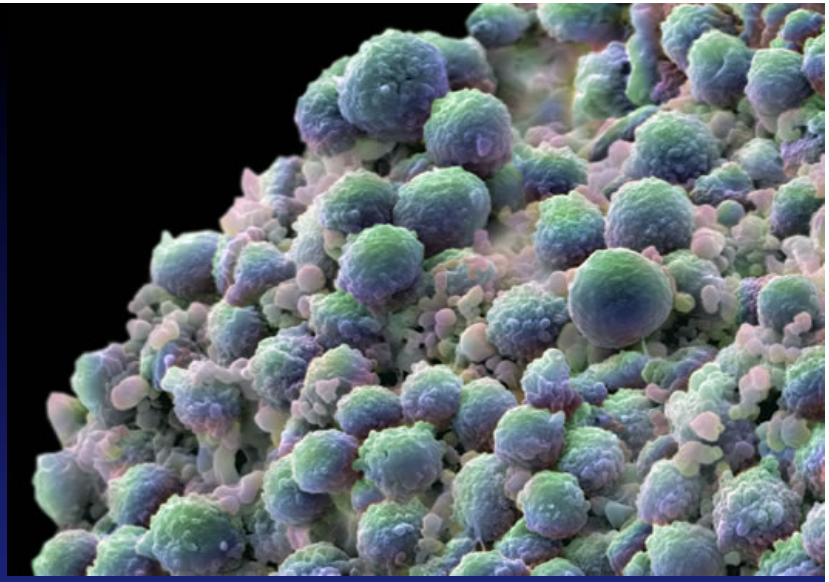
- Cancer is not one thing
- Not one cause, not one gene signature
- Cell reg. mechanisms vastly complex
- Treatments better, not good
- Time to ask new evolutionary questions
  - How do cancers evolve?
  - Why didn't natural selection make us less vulnerable?

What does evolution offer?

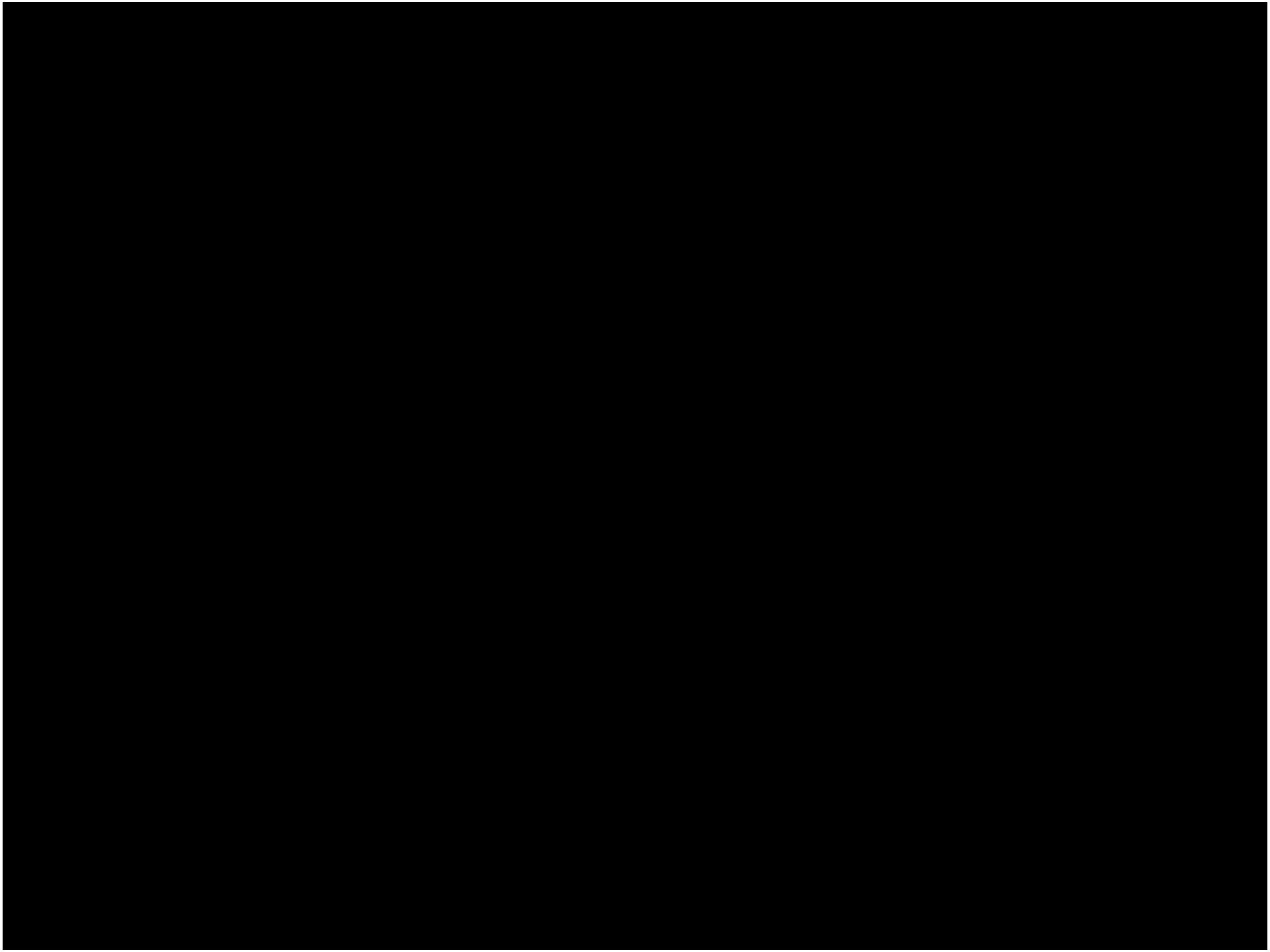
- Somatic evolution in tumors
- Social evolution theory
- Contributions of Darwinian medicine
- Bodies are not machines



Tumor evolution



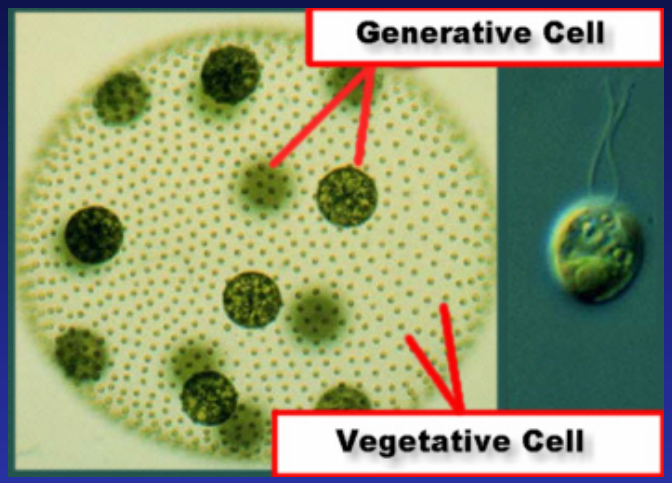
- Genetic data
- Theoretical foundation
- Progress coming fast
- Practical implications
- Better theory still needed



Social Evolution Theory

- We now understand how selection shapes cooperation
- Powerful applications in cancer biology
- Much more to do!
- The Synergistic duo!

Problems for Metazoans



- Connection
- Orientation
- Differentiation
- Prevent undifferentiation
- Control defectors
- Sequester reproductive from somatic
- Nourishment, excretion, coordination…
- SOCIAL problems!

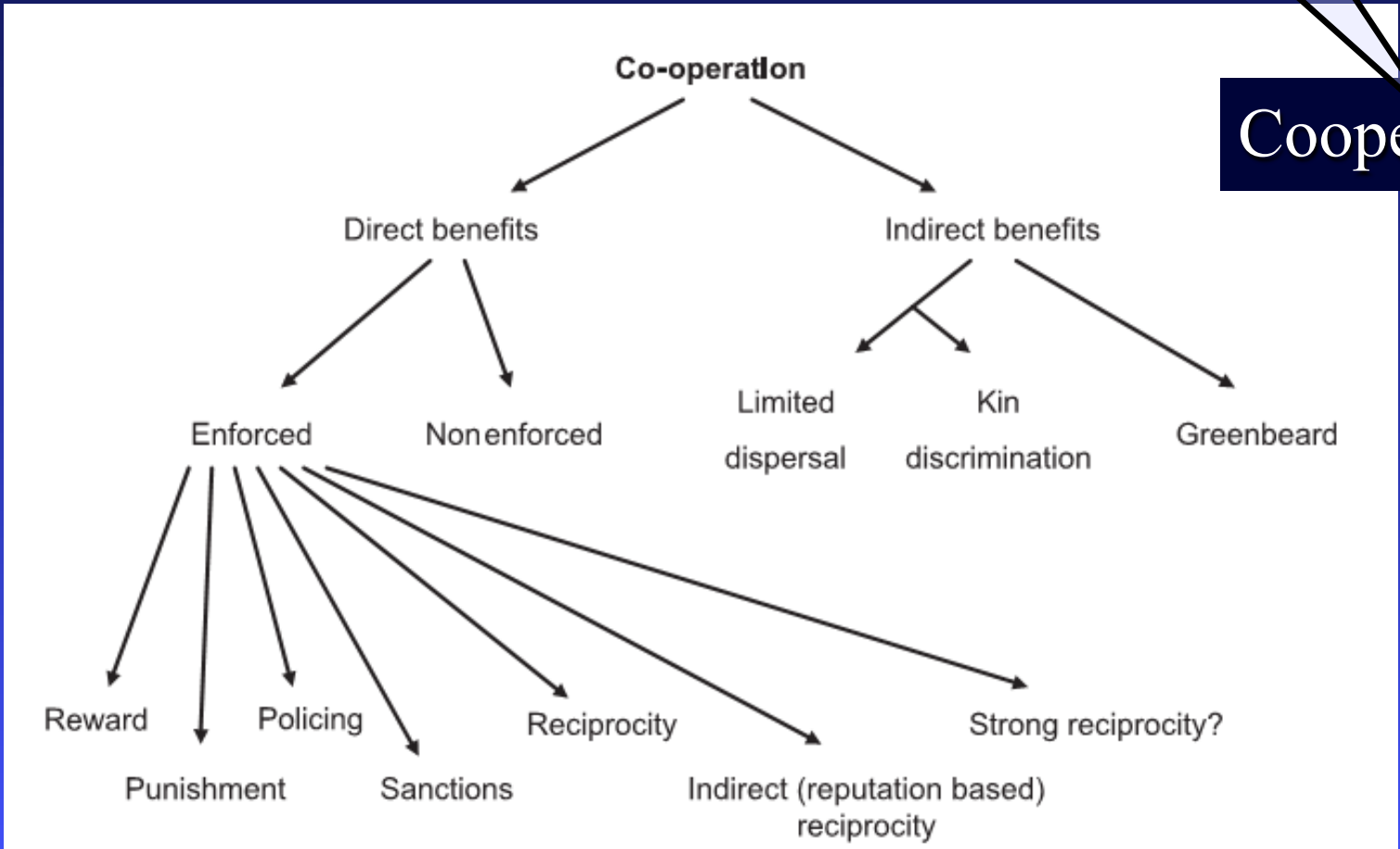
Semantic confusion

West et al., 2006, 2007

		Effect on recipient +	Effect on recipient −
Effect on actor	+	Mutual benefit	Selfishness
Effect on actor	−	Altruism	Spite

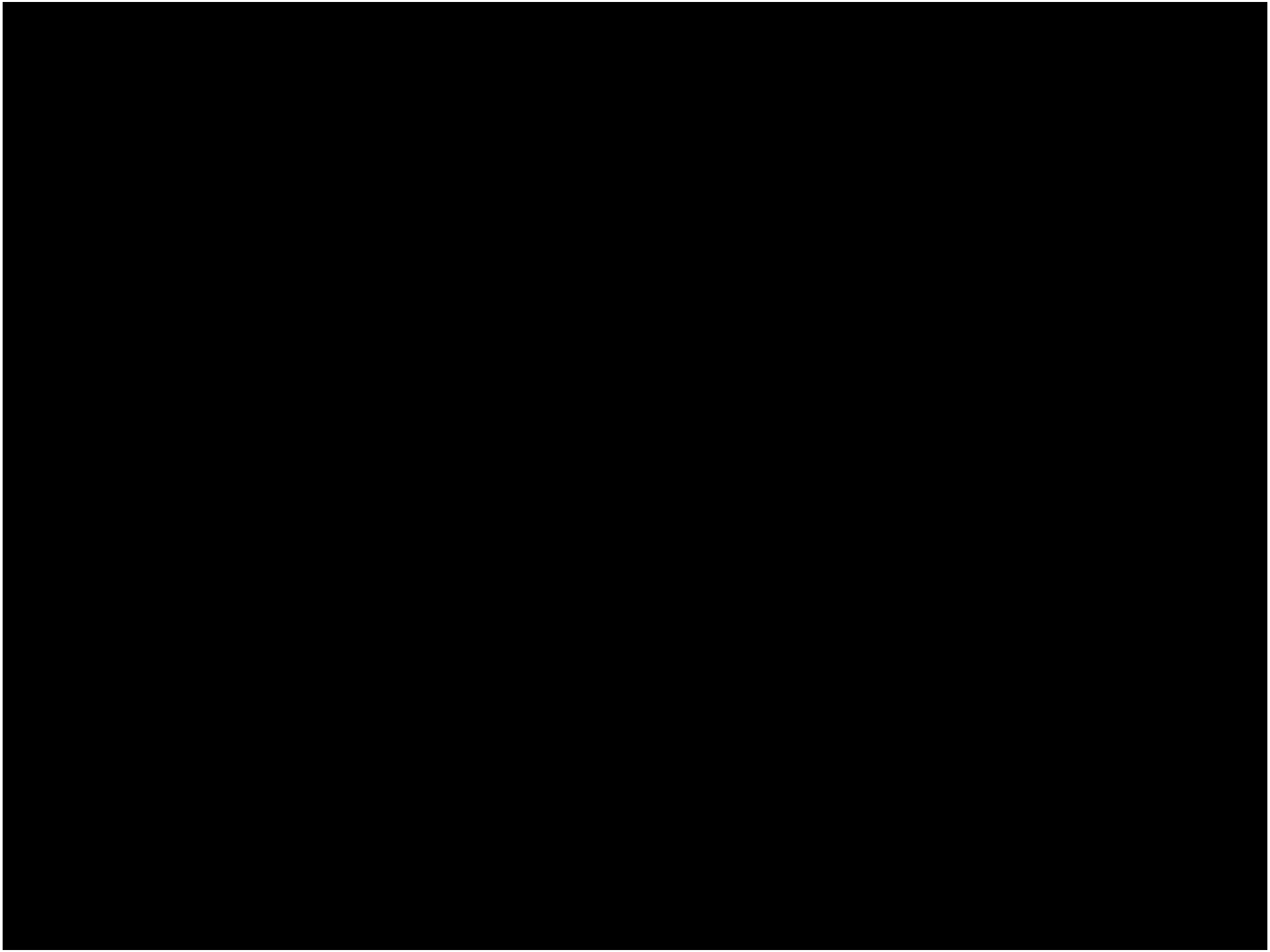
Current Biology

Cooperation



Research questions

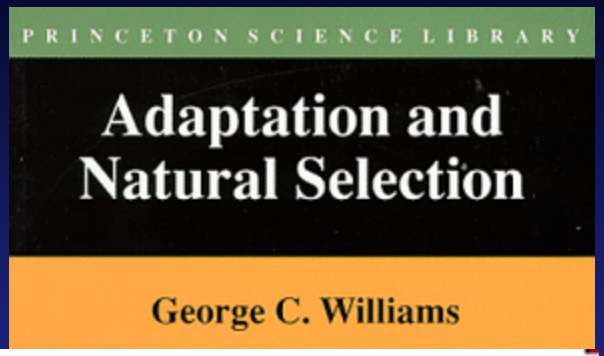
- How to explain cooperation that controls cell proliferation?
- How to explain social life of cells in a tumor?
- Why isn’t cancer more common?

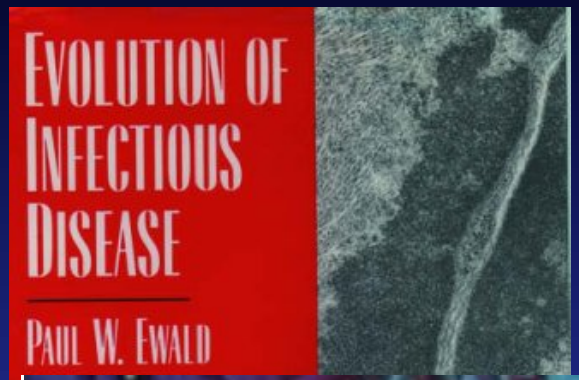


Darwinian Medicine

- The field that applies the basic science of evolutionary biology to the problems of medicine and public health.
  - Analogous to genetic medicine
- Not a method of practice
- Not opposed to ordinary medicine

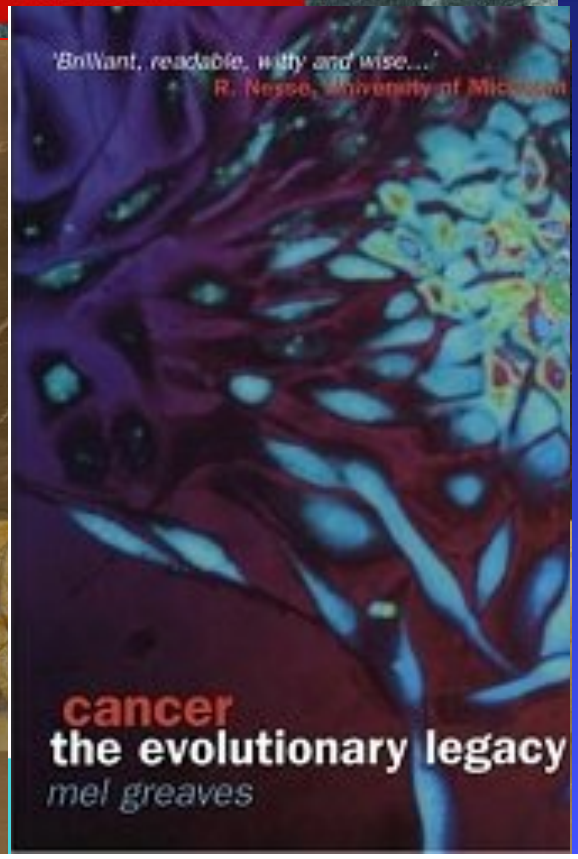
Progress

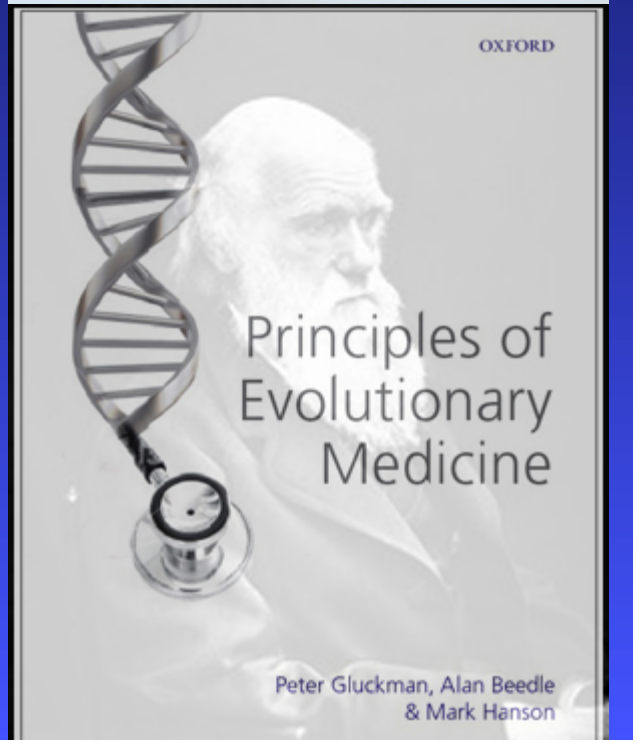

PRINCETON SCIENCE LIBRARY
Adaptation and Natural Selection
George C. Williams


Evolution of Infectious Disease
Paul W. Ewald


Evolutionary Medicine and Health
New Perspectives


PNAS
Evolution in Health and Medicine
GEORGE C. WILLIAMS, PH.D.


cancer
the evolutionary legacy
mel greaves


OXFORD
Principles of Evolutionary Medicine
Peter Gluckman, Alan Beedle & Mark Hanson

Organizations advancing evolutionary medicine

- NEScent
- MDIBL
- IOM
- NAS
- SSE

The Evolution and Medicine Review
http://evmedreview.com

Mount Desert Island Biological Laboratory
Summer Course on Evolution and Medicine
August 2-8, 2011

Standards of Evidence

- Nesse: *Ten Questions to ask about Evolutionary Studies of Disease*
  - Evolutionary Applications, 2011

Four lines of work

Nesse & Stearns, 2008

1. **Infection**
2. **Phylogenies**
3. **Evolutionary genetics**
4. **Why selection left our bodies vulnerable**

The body is not a machine

FIVE OBJECTS OF EXPLANATION	TWO KINDS OF EVOLUTIONARY QUESTIONS	
	PHYLOGENY	**ADAPTIVE SIGNFICANCE**
Human trait	**Phylogeny of traits** Lactase persistence, Ethanol sensitivity, Blood types, HLA types Skin color, Malaria resistance	**Adaptive significance of traits** Aging, Bilirubin Narrow birth canal, Fever, Cough, Anxiety Stress response
Human gene	**Tracing the phylogeny of alleles that cause disease** Sickle cell disease Cystic fibrosis, ApoE Asthma vulnerability alleles	**Possible adaptive significance of alleles that cause disease** Sickle cell disease Cystic fibrosis, ApoE Asthma vulnerability alleles
	Population genetics, Evolutionary genetics, Signals of selection	
Pathogen trait	**Evolutionary history of pathogen traits** Virulence, Antibiotic resistance, Ability to survive outside the body, Biofilm formation	**Possible adaptive significance of pathogen traits** Virulence, Antibiotic resistance, Ability to survive outside the body, Biofilm formation
Pathogen gene	**Tracing the phylogeny of pathogen alleles** Tracing and predicting influenza subtypes, Source of food poisoning, HIV evolution	**Possible adaptive significance of pathogen alleles** Alleles that influence virulence, Antibiotic resistance, Biofilm formation, Spore formation
Cell lines	**Cancer**	**Immune system cells**

Nesse & Stearns, *Evolutionary Applications*, 2008

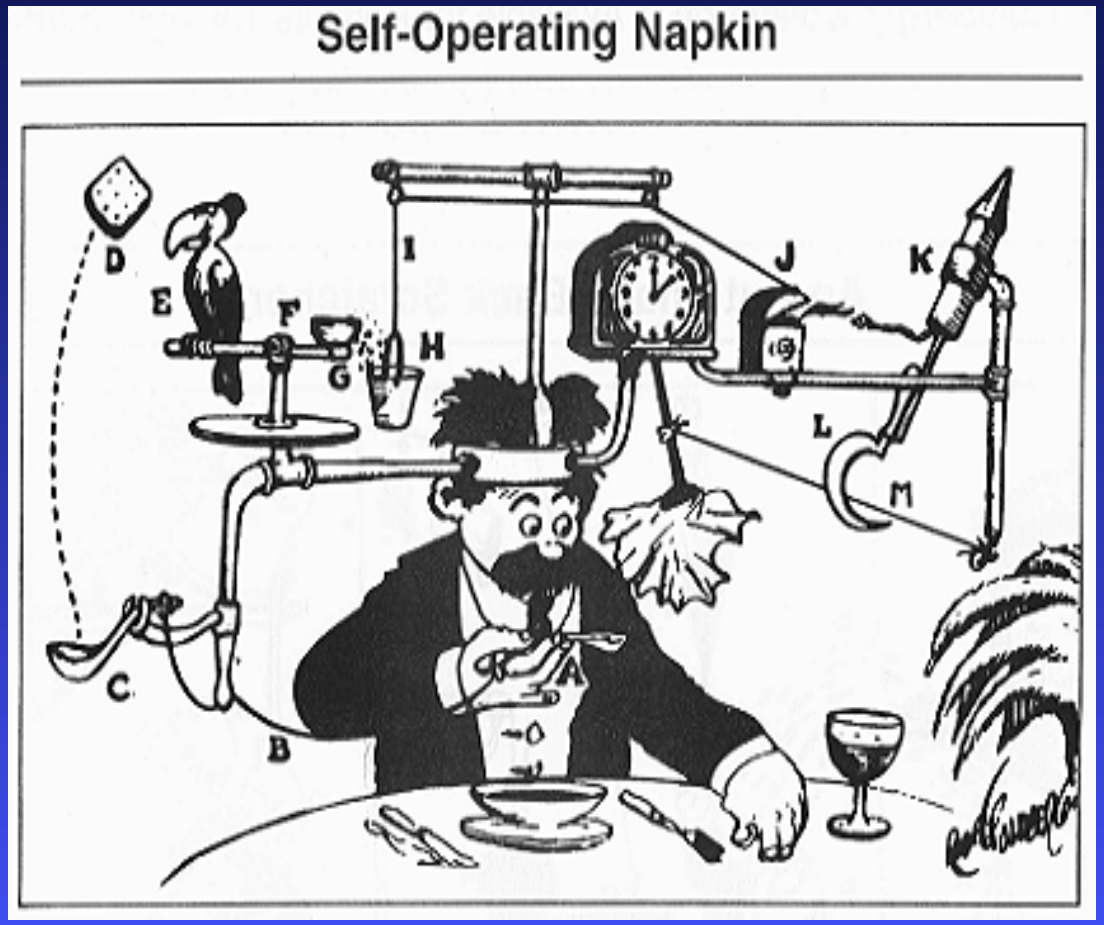
FIVE OBJECTS OF EXPLANATION	TWO KINDS OF EVOLUTIONARY QUESTIONS	
	PHYLOGENY	**ADAPTIVE SIGNFICANCE**
Human trait	Phylogeny of human traits	Adaptive significance of traits Inflammation
Human gene	Phylogeny of human alleles	Adaptive significance of alleles e.g. p53
	Population genetics, Evolutionary genetics, Signals of selection	
Pathogen trait	Phylogeny of pathogen traits	Adaptive significance of traits Cell division induction
Pathogen gene	Phylogeny of pathogen alleles	Adaptive significance of alleles
Cell line traits	Angiogenesis, independence, etc.	**Tumor traits**
Cell line genes	Somatic mutations	Functions of tumor mutations

Nesse & Stearns, *Evolutionary Applications*, 2008

Q: Why has selection left us vulnerable to cancer?

- Not why some people get cancer
- Not a description of mechanisms
- But why we all are vulnerable

The Old Answer: Natural selection is just too weak to make the body better.



The New Answer

- **Six reasons** why natural selection leaves bodies vulnerable to disease
- Ask EVOLUTIONARY questions

Six Reasons Why Diseases Exist

1. **Mismatch: body in a novel environment**
2. **Competition with fast evolving organisms**
3. **Every trait is a trade-off**
4. **Constraints on natural selection**
5. **Organisms shaped for R/S, not health**
6. **Defenses and suffering**

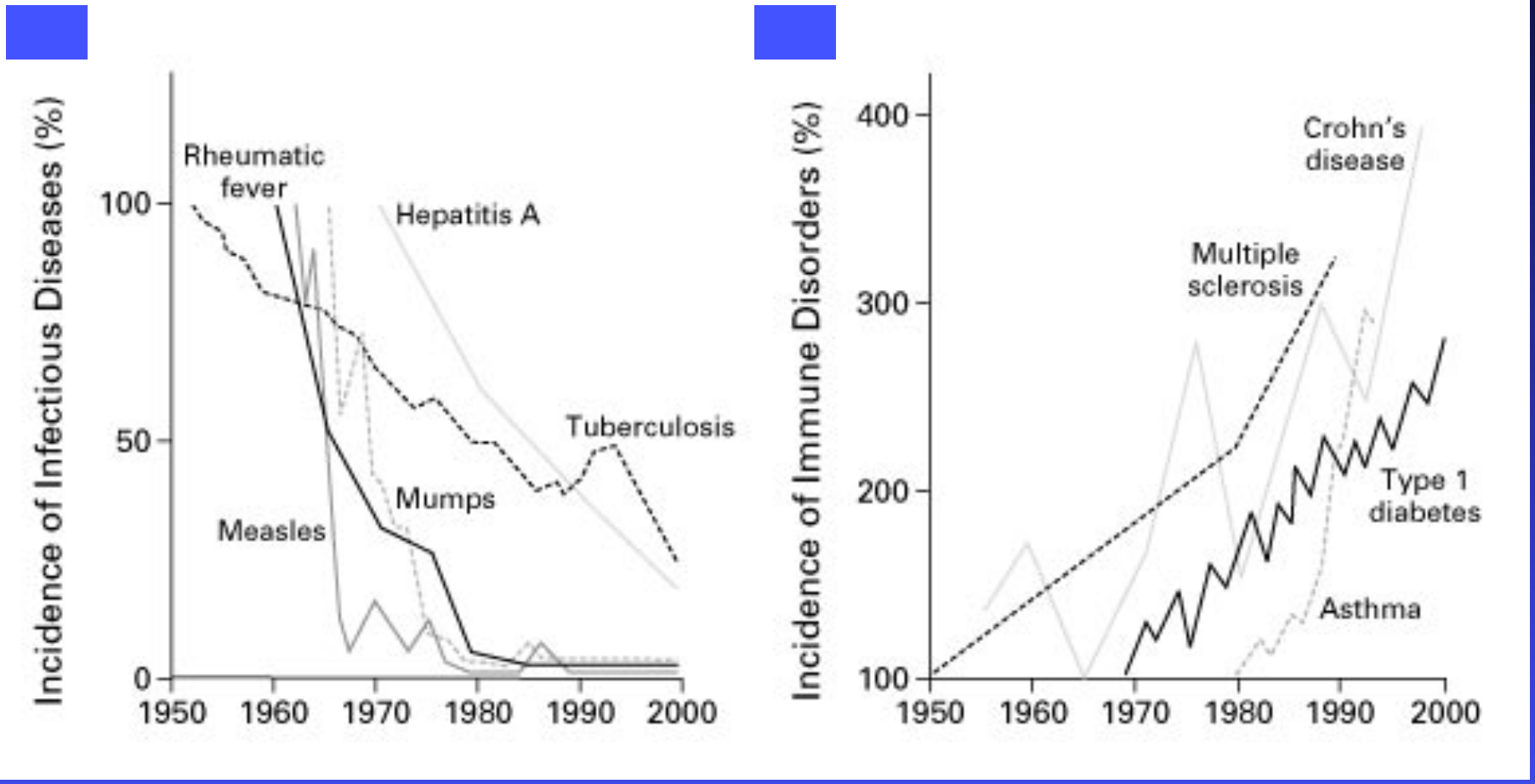
1. Mismatch

Changes since agriculture 10,000 y

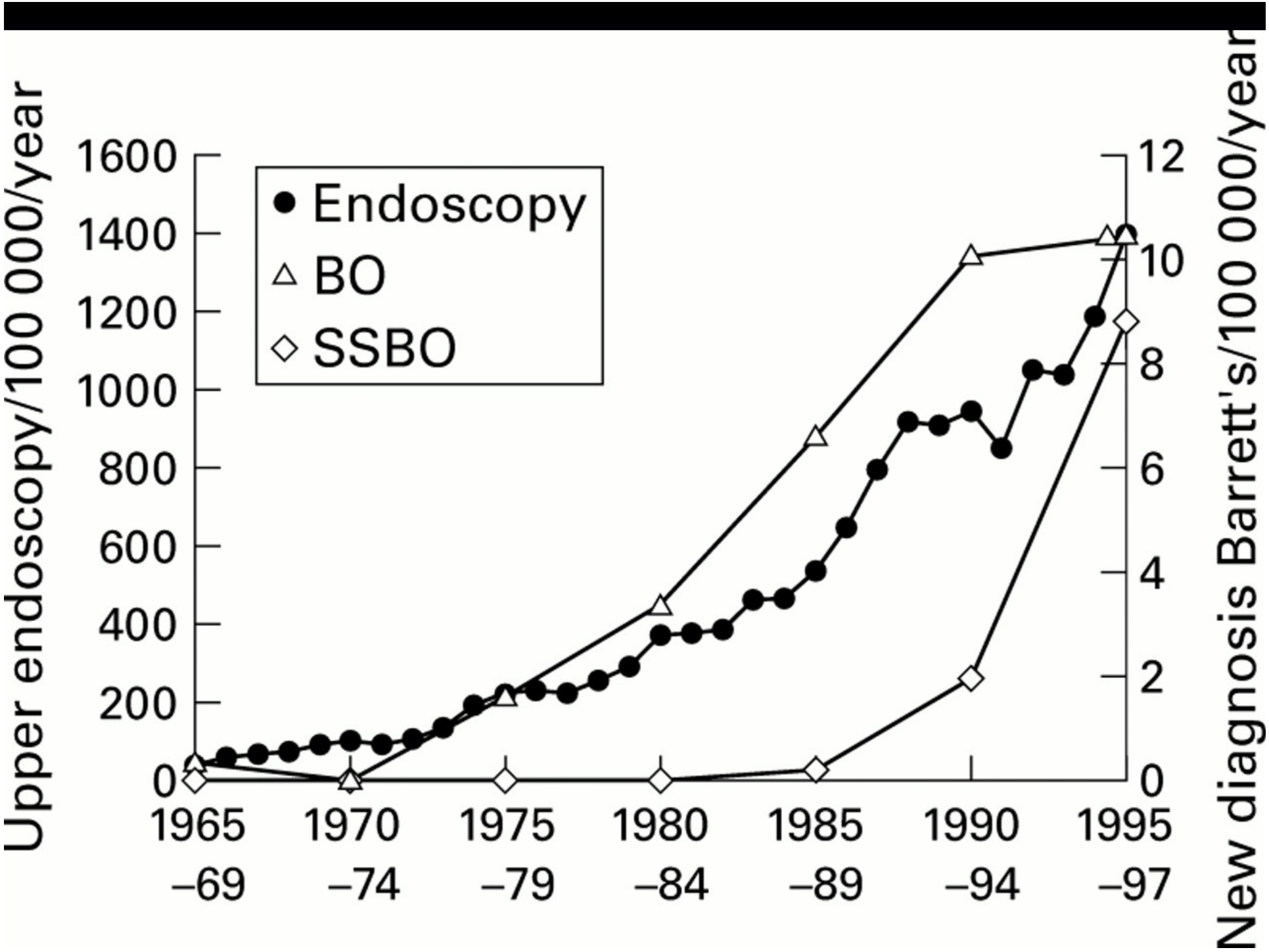
Changes since industrialization 200 y

Changes since technology 50 y

The ‘Epidemiological Transition’



Bach 2002 NEJM 347(12):912


Upper endoscopy/100 000/year
New diagnosis Barrett's/100 000/year
Endoscopy
BO
SSBO
1600
1400
1200
1000
800
600
400
200
0
12
10
8
6
4
2
0
1965 –69
1970 –74
1975 –79
1980 –84
1985 –89
1990 –94
1995 –97

Breast Cancer

- 10x more common now
  - Hormone exposure (Eaton, Strassmann)
    - 400+ cycles now, about 110 then
  - Night light exposure
    - Melatonin

More menstrual cycles now

Strassmann, 1999

Lifetime cycles

Dogon 100

USA 300+

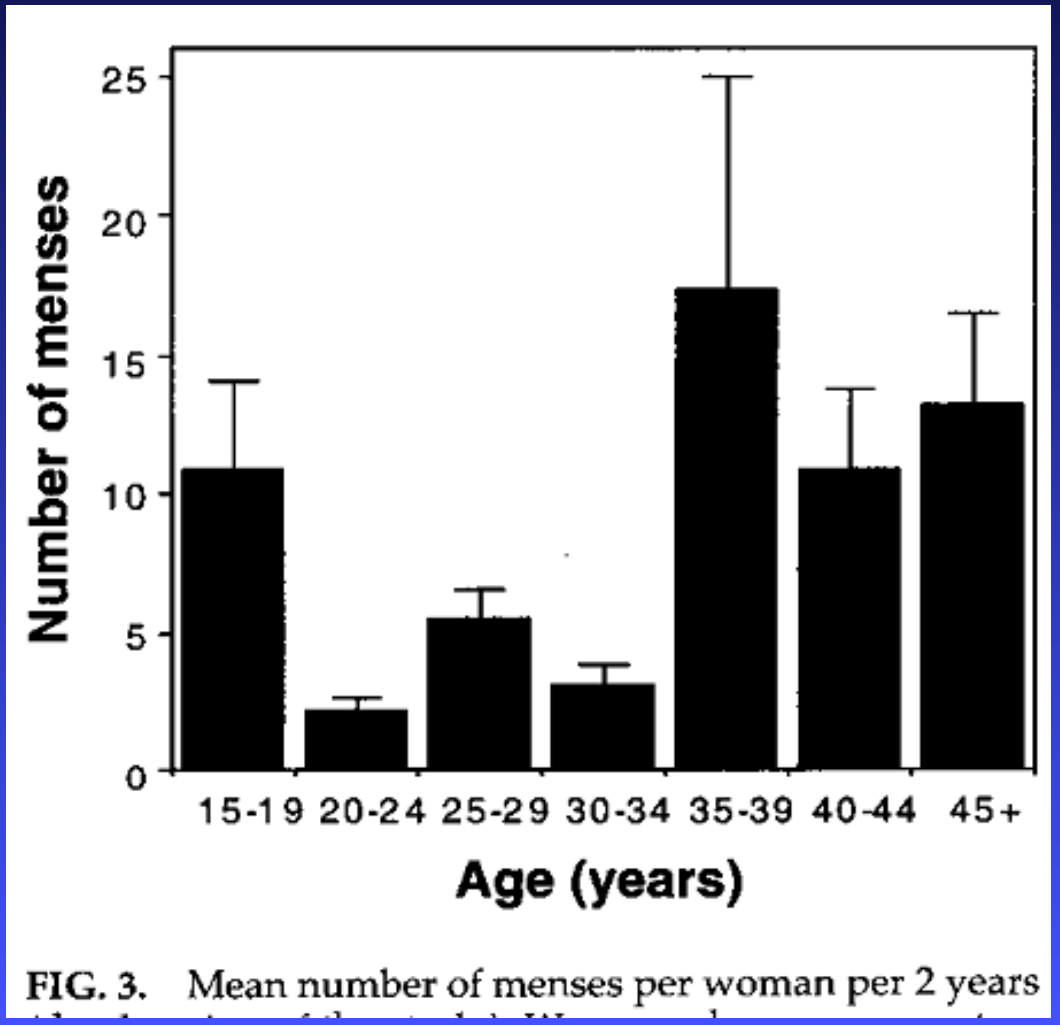
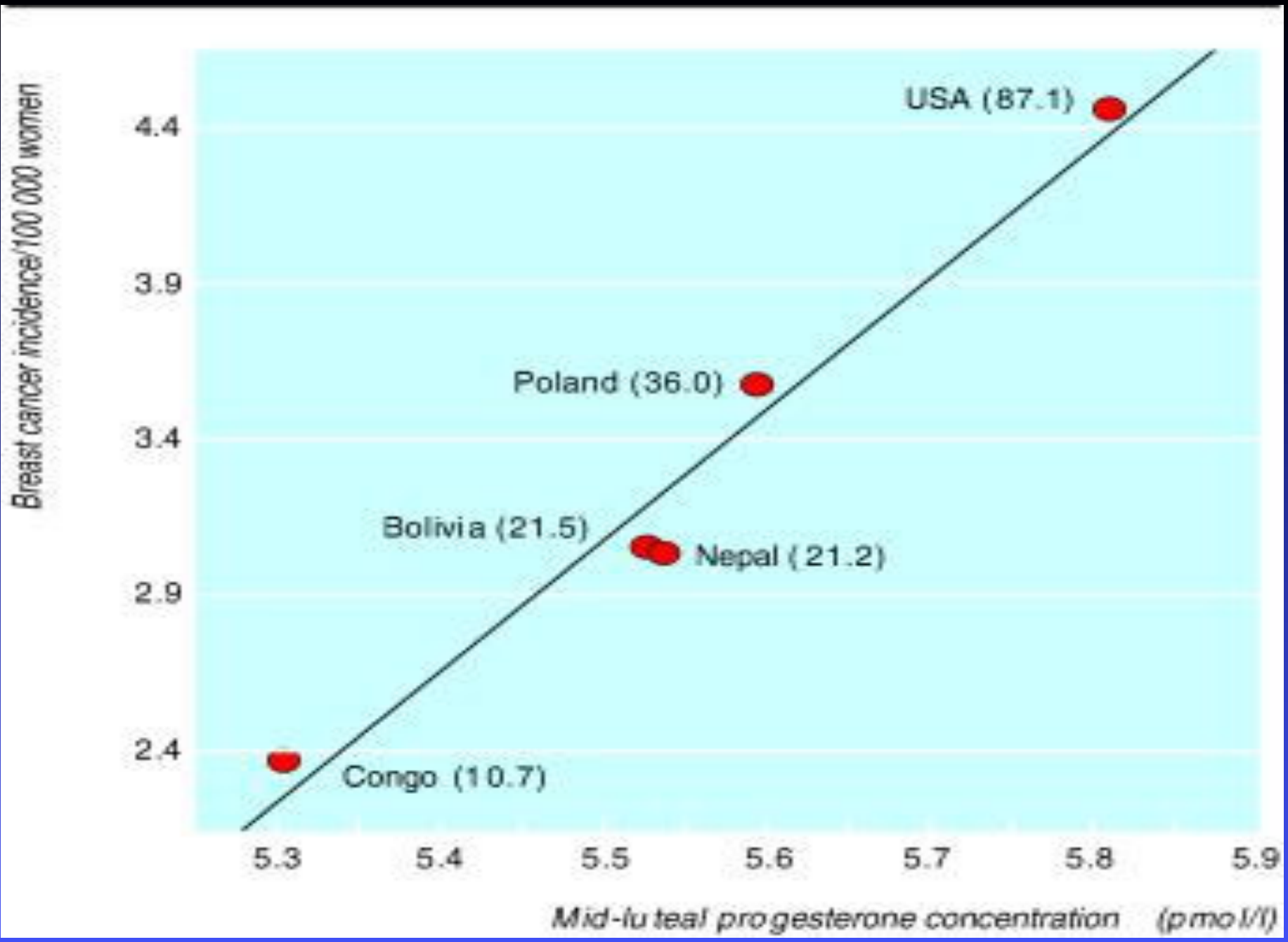


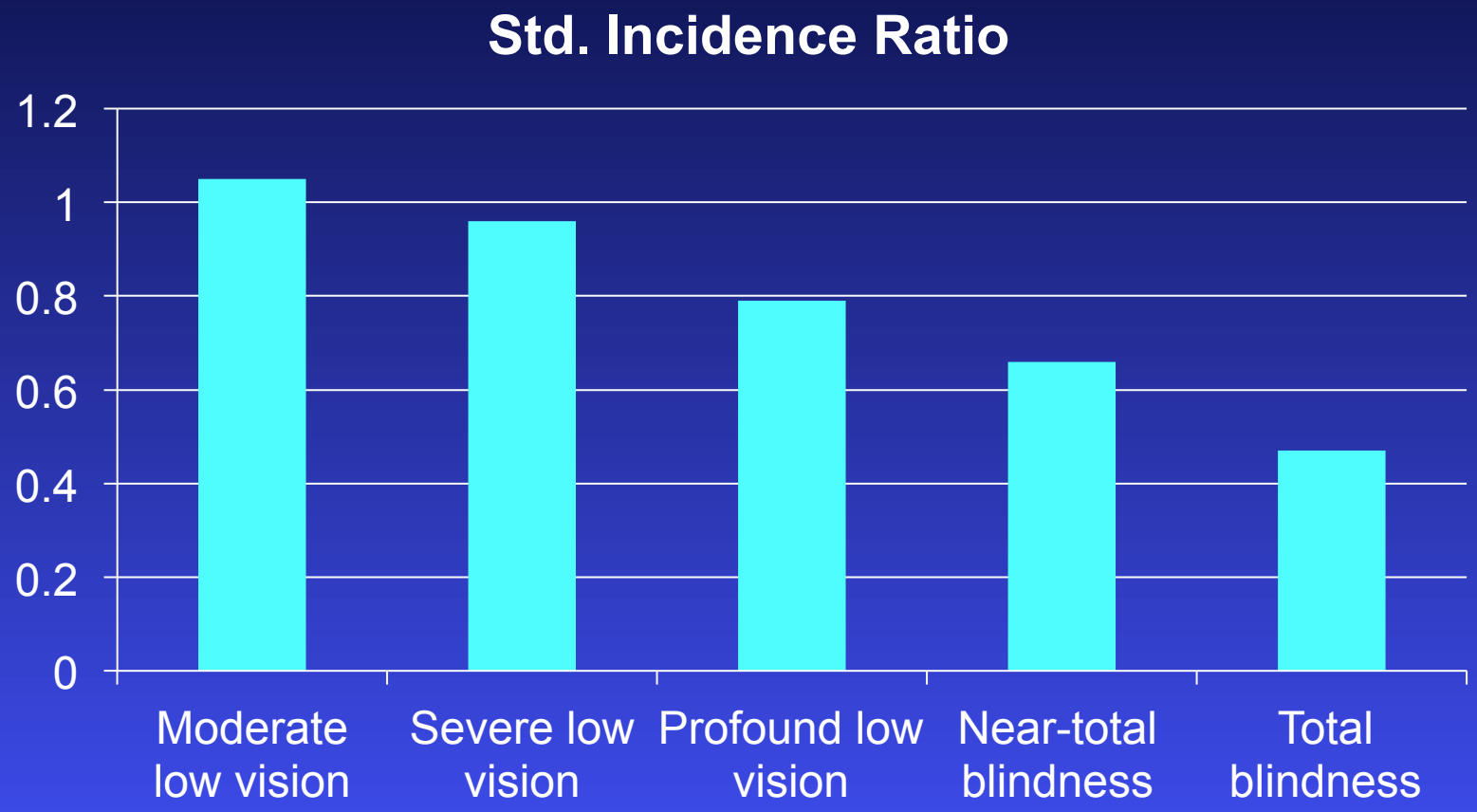
FIG. 3. Mean number of menses per woman per 2 years


Breast cancer incidence/100 000 women
4.4
3.9
3.4
2.9
2.4
USA (87.1)
Poland (36.0)
Bolivia (21.5)
Nepal (21.2)
Congo (10.7)
5.3
5.4
5.5
5.6
5.7
5.8
5.9
Mid-luteal progesterone concentration (pmol/l)

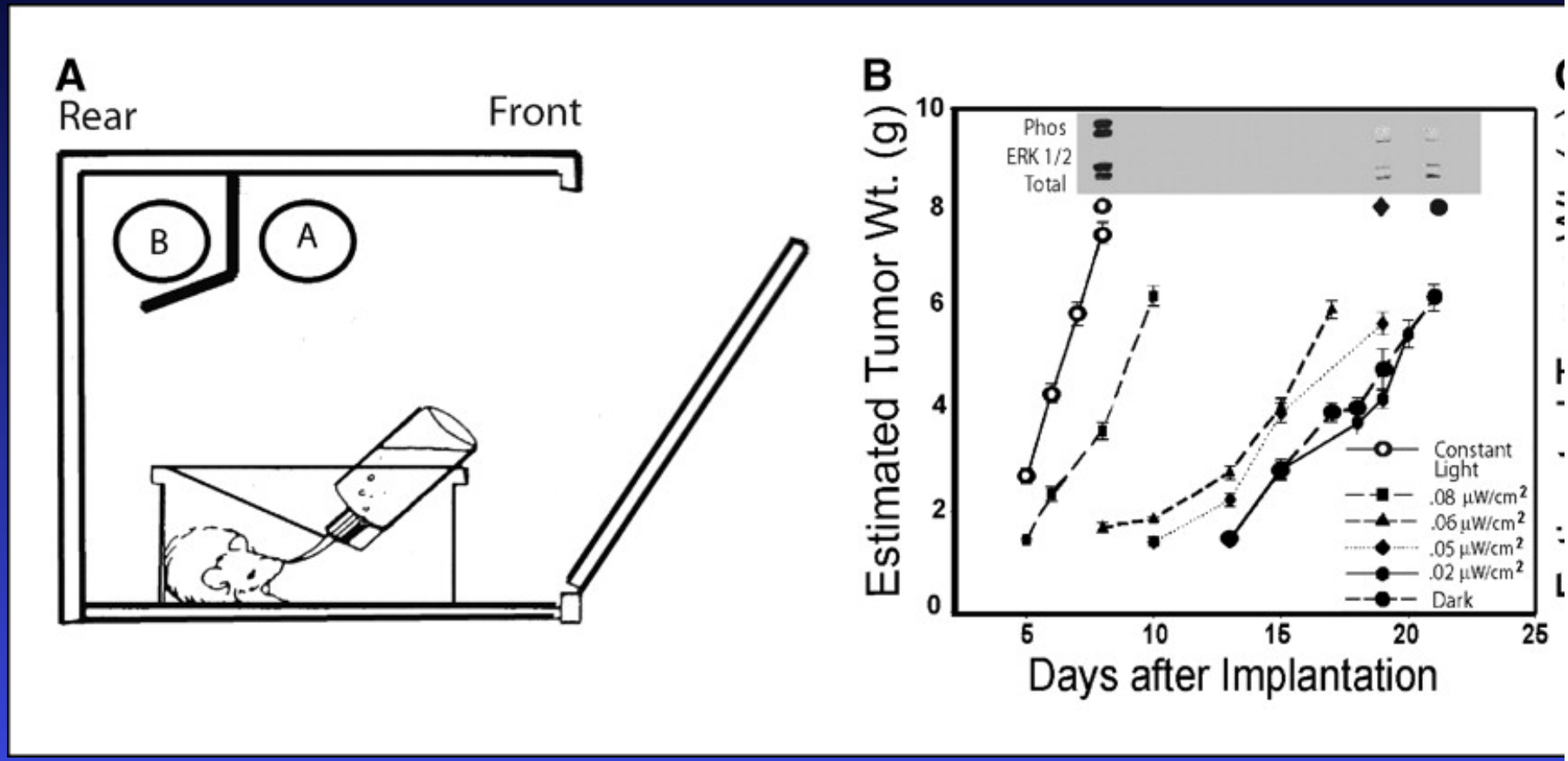
Modern sleep & light at night

Breast cancer in blind women

Verkasalo, 1999



Ocular exposure of tumor-bearing rats to light during darkness.



Blask D E et al. Cancer Res 2005;65:11174-11184

Increased inflammation?

- Lack of helminths/infection→
- Decreased immune inhibitors →
- Increased inflammation (x10?) →
- Cell damage →
- Cancer

Other environmental novelties

- Hygiene → Childhood leukemia
- Toxins PCBs, etc. → Liver etc.
- Radiation exposure
- Tobacco→ Lung

Research Questions

- Cancer rates in ancestral environment?
- Does lack of helminths increase inflammation that causes cancer?
- Can melatonin slow cancer progression?
- What other novel factors are we missing?

2. Competition with other organisms

(Paul Ewald and others have explained)

- Pathogens that induce cell division
- Insertion of genetic sequences
- Arms races and costly defenses
  - Inflammation

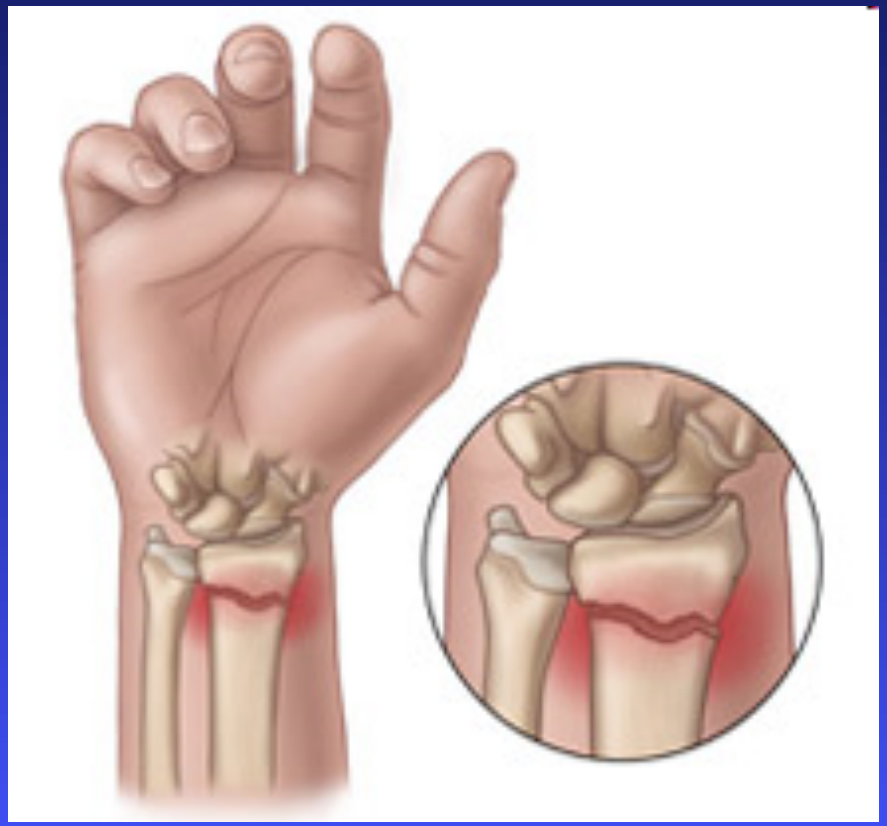
Research questions

- Do some biomes → cancer?
- What strategies lead some pathogens to induce cell division?
- Why aren't mechanisms that repress expression of viral sequences better?
- Does lack of infection change immune responses in ways that cause cancer?

3. Every trait is a trade-off

Nothing in the body can be perfect

Colles fracture

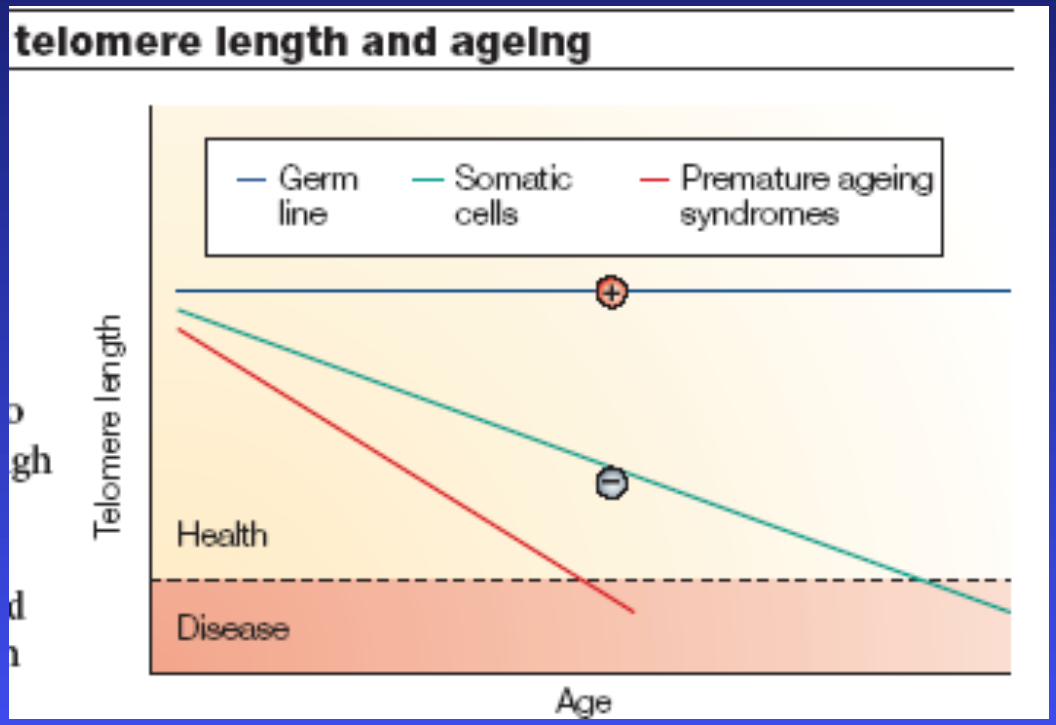


Tradeoffs and cancer

- Costs of better cancer defenses
  - Faster aging
  - More energy use
- Telomere length
  - Aging vs. cancer susceptibility
- Inflammation intensity
  - Infection protection vs. cancer

Antagonistic Pleiotropy

Blasco, 2005



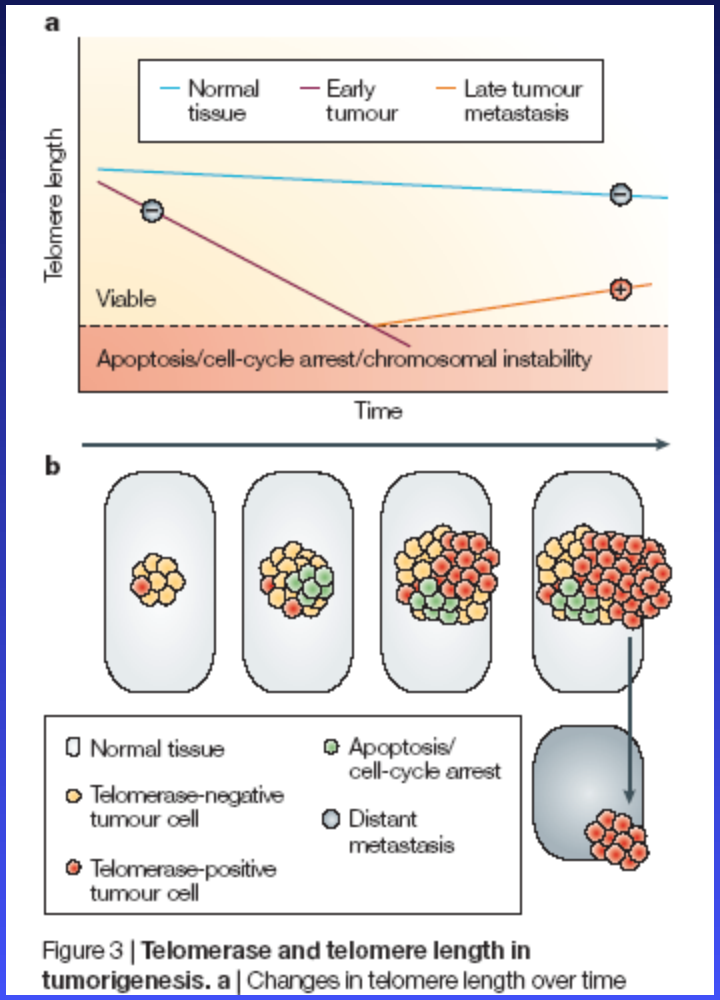


Figure 3 | **Telomerase and telomere length in tumorigenesis. a** | Changes in telomere length over time

Research Questions

- What disadvantages are associated with decreased cancer vulnerability?
- Reproduction vs. cancer protection
- Why are some tissues more vulnerable?

4. **Constraints**

- Mutations happen
  - Repair is limited—and can cause new problems
- Cell cycle regulation is imperfect
- Tumors evolve!

Research Question

- What is cancer rate for those with good genes in the natural environment?
- No specific cause for some cancers, just stupid stochasticity
- What tradeoffs limit cancer protection?

5. Health is not selection's goal

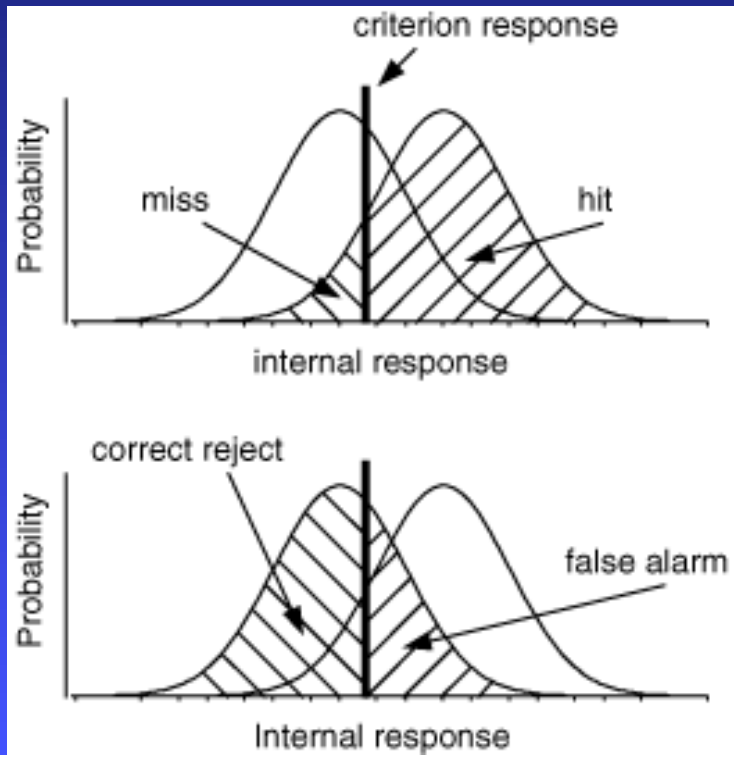
- Selection maximizes reproduction, NOT health, longevity, & happiness
- ? Reproductive cancers?
- Athena's talk: early advan→ later cost

6. Defenses

- Inflammation and other defenses damage cells
- Defenses against cancer must be extremely costly

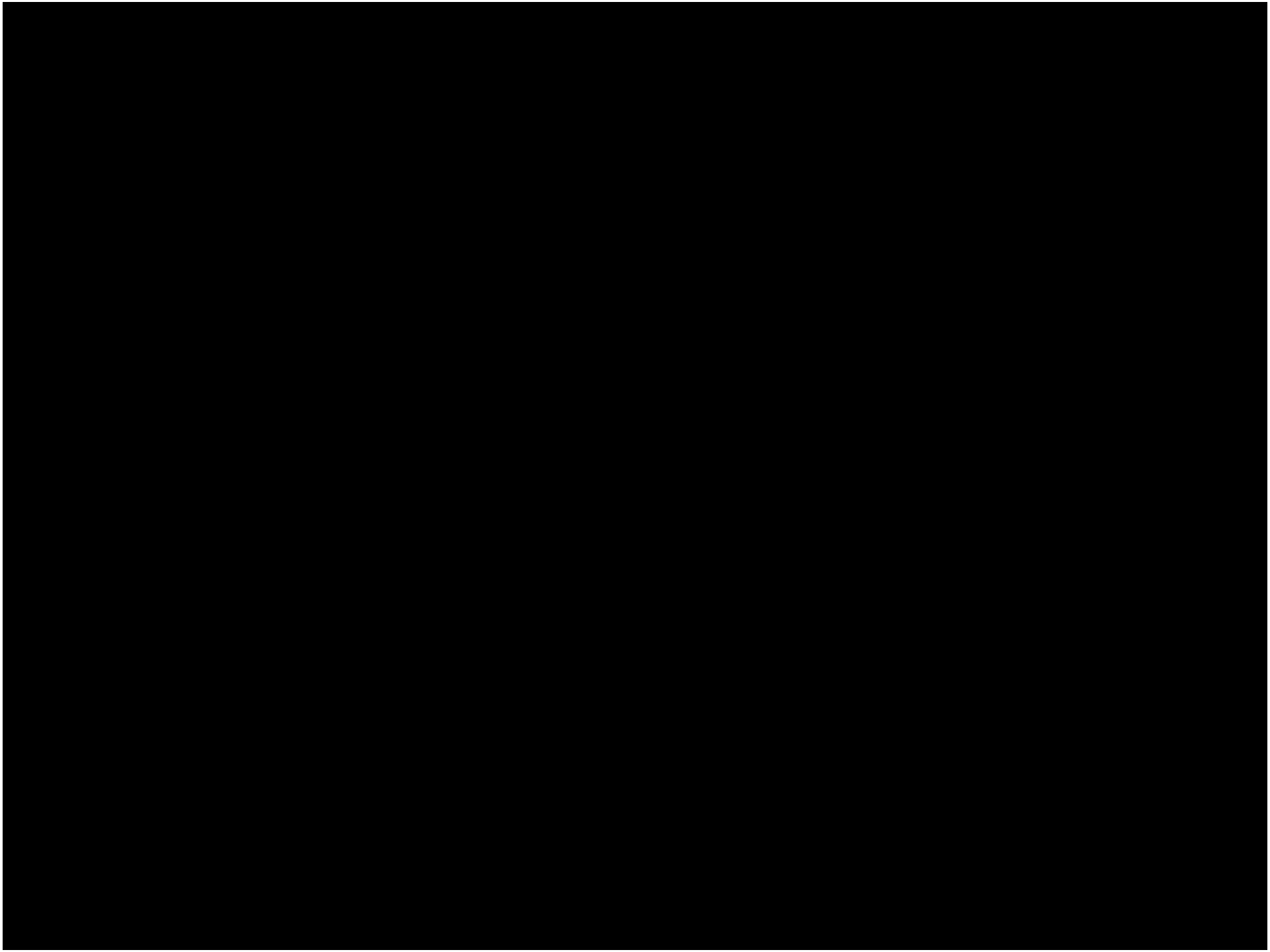
Smoke Detector Principle

- Defenses expressed readily because they are cheap compared to risk of catastrophic failure
  - Still cause damage
- Defenses against cancer
  - Big costs (to discover)



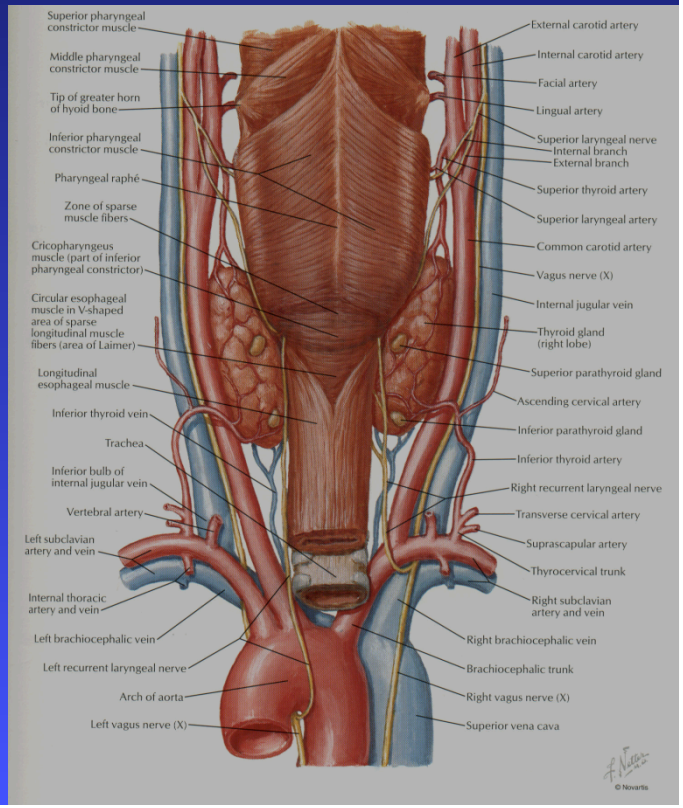
Six Reasons Why Diseases Exist

1. **Mismatch: body in a novel environment**
2. **Competition with fast evolving organisms**
3. **Every trait is a trade-off**
4. **Constraints on natural selection**
5. **Organisms shaped for R/S, not health**
6. **Defenses and suffering**



The Body is NOT a Machine

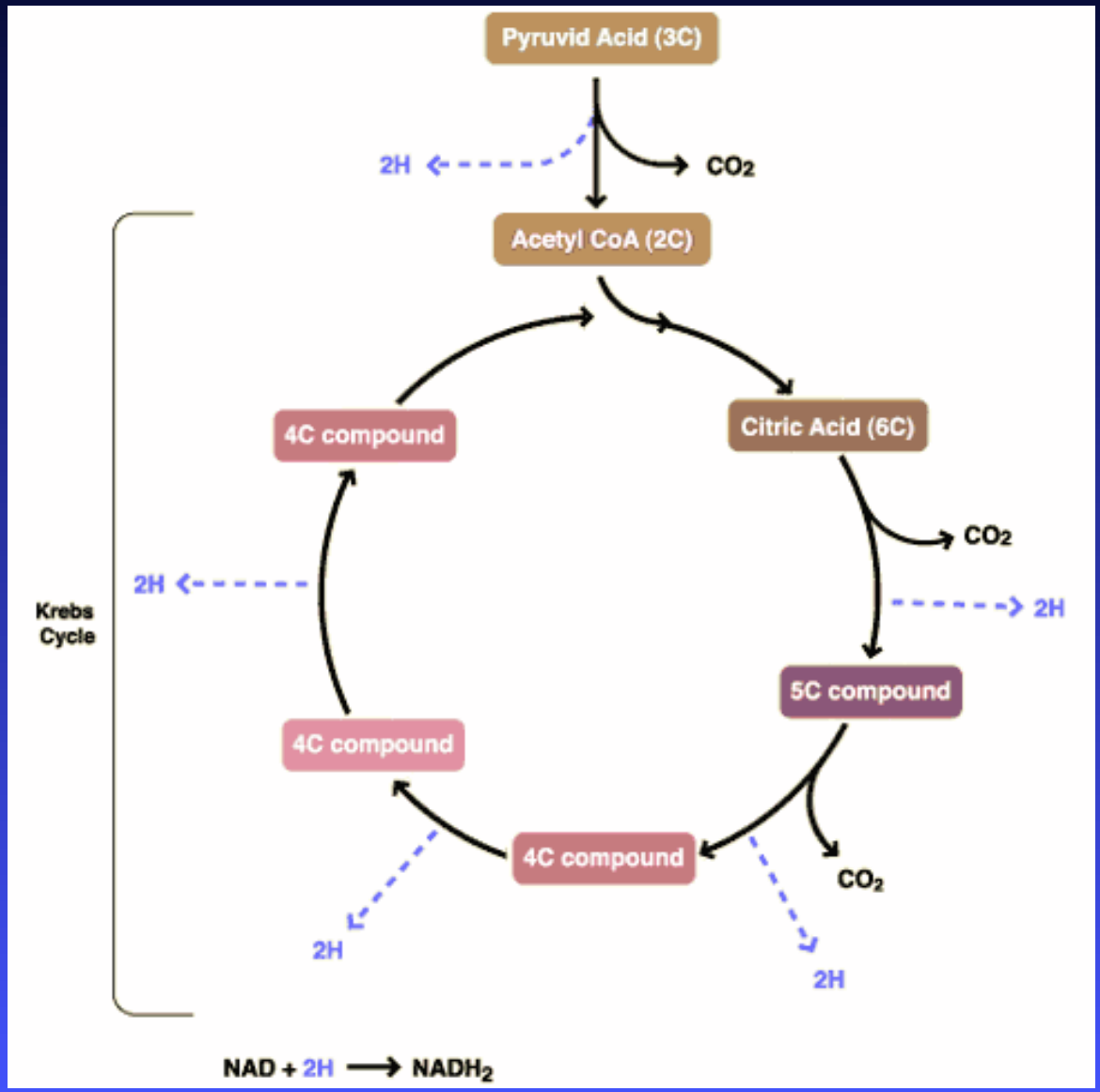
- Not designed
  - Discrete parts with
  - Specific functions
- Shaped by selection
  - Some mechanisms indescribably complex

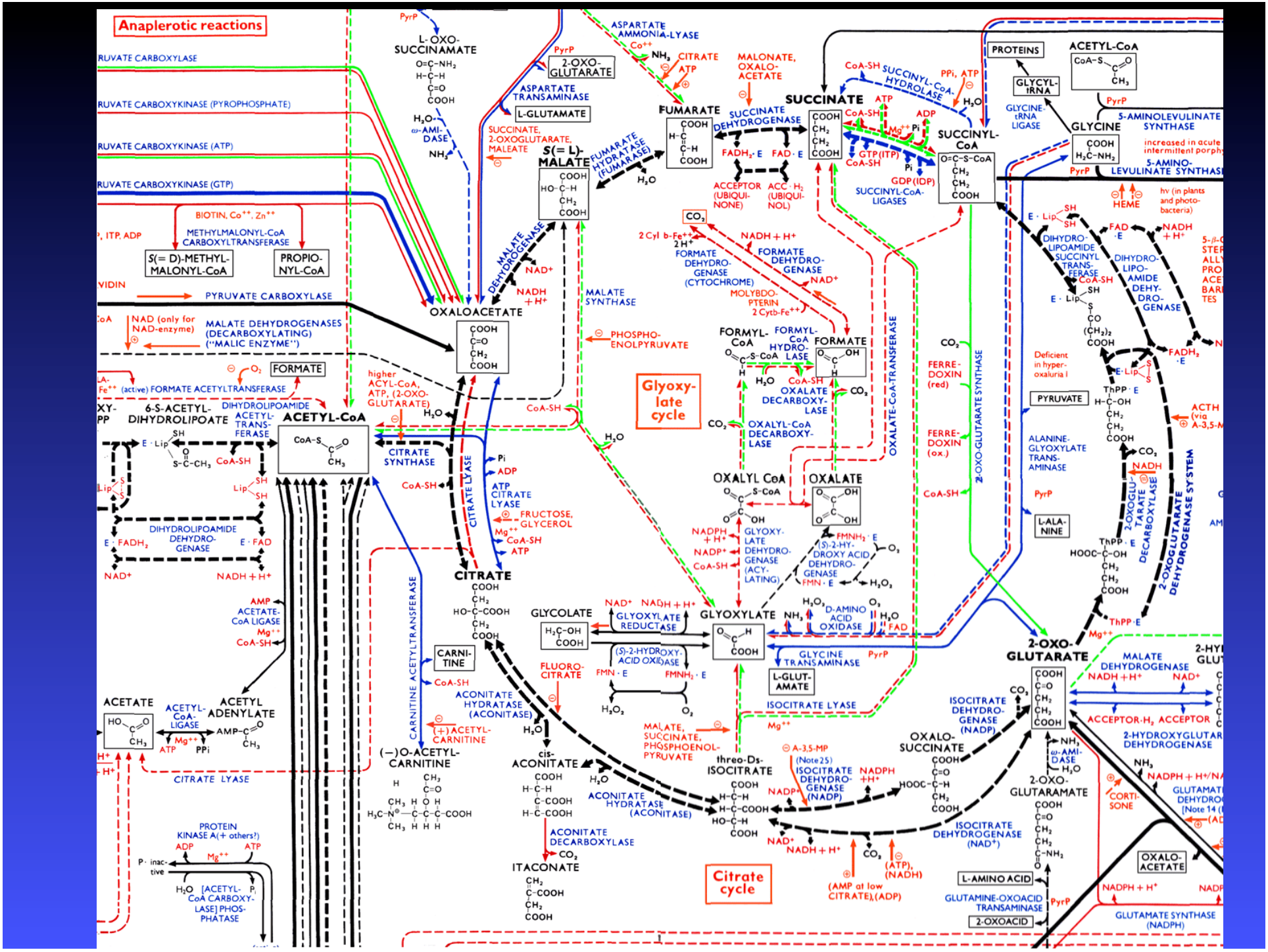


Organic Complexity

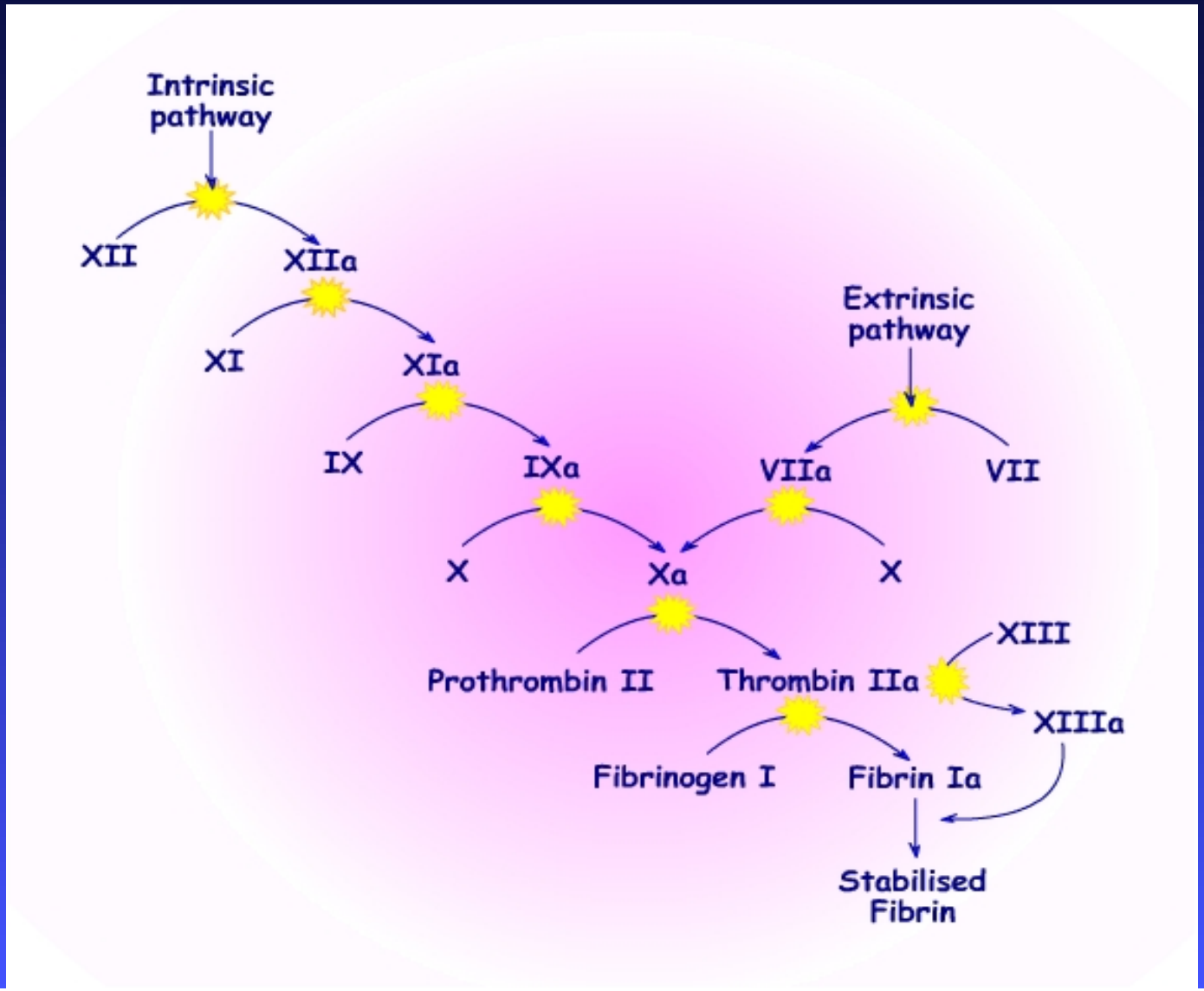
- Machines: Discrete components with specific functions
- Bodies: Distributed functions arising from systems organically complex in ways fundamentally different from machines

Krebs Cycle

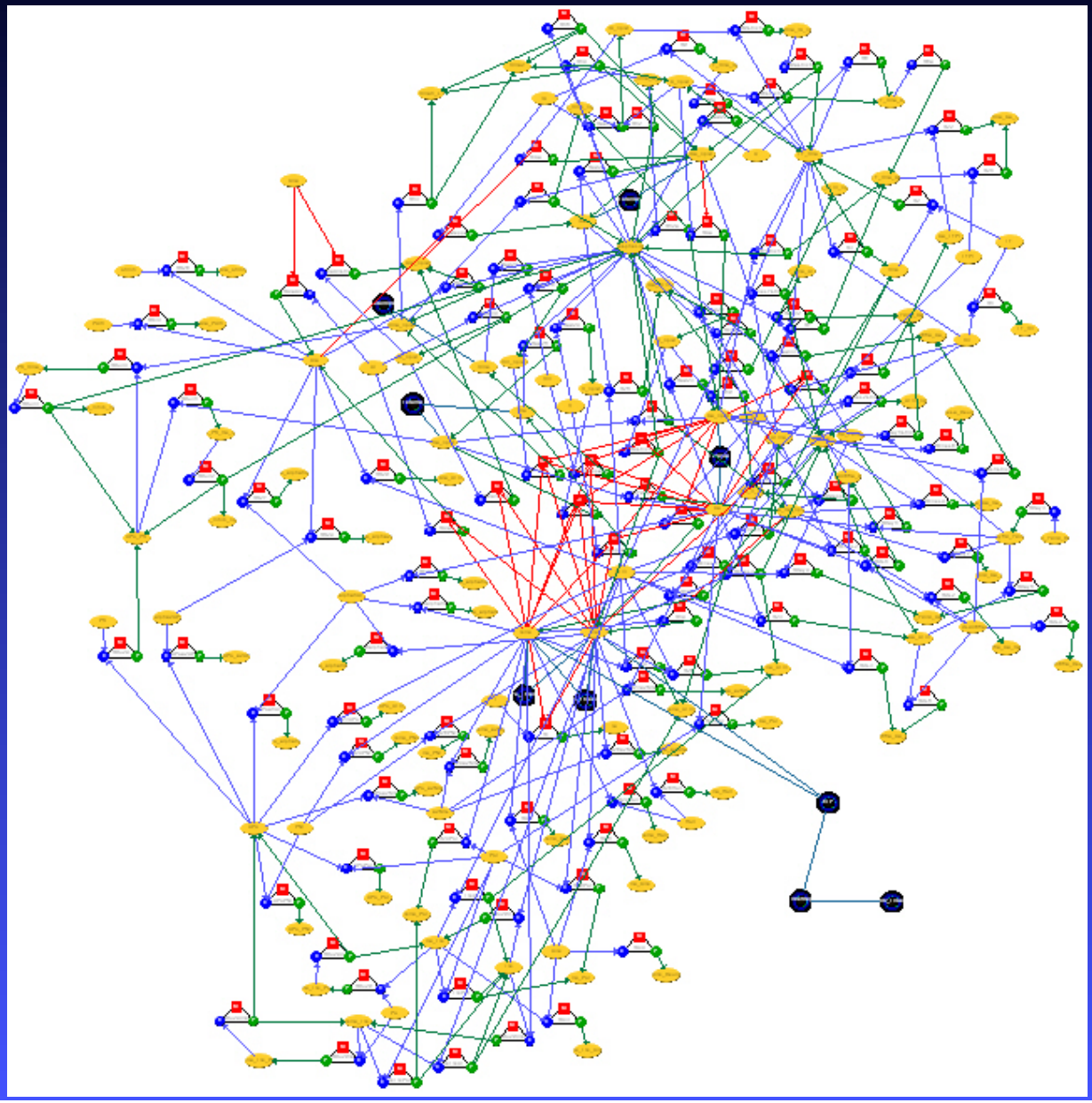

Pyruvid Acid (3C)
2H
CO_2
Acetyl CoA (2C)
Citric Acid (6C)
CO_2
2H
5C compound
CO_2
2H
2H
4C compound
4C compound
2H
4C compound
Krebs Cycle
NAD + 2H ⟶ $NADH_2$

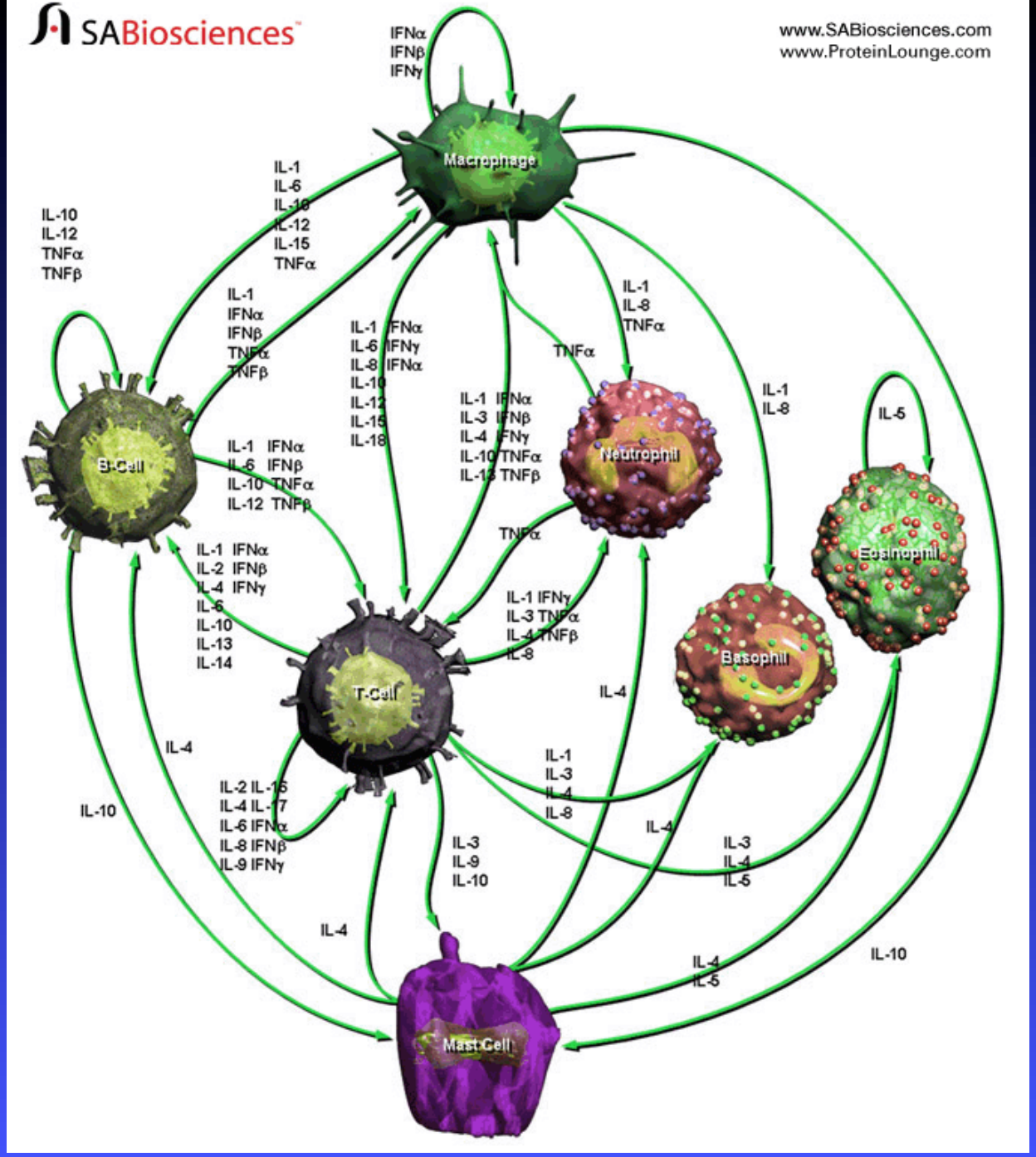

Anaplerotic reactions
RUVATE CARBOXYLASE
RUVATE CARBOXYKINASE (PYROPHOSPHATE)
RUVATE CARBOXYKINASE (ATP)
RUVATE CARBOXYKINASE (GTP)
, ITP, ADP
VIDIN
PYRUVATE CARBOXYLASE
BIOTIN, Co++, Zn++
METHYLMALONYL-CoA CARBOXYLTRANSFERASE
S(= D)-METHYL-MALONYL-CoA
PROPIO-NYL-CoA
NAD (only for NAD-enzyme)
MALATE DEHYDROGENASES (DECARBOXYLATING) ("MALIC ENZYME")
OXALOACETATE
PyrP
L-OXO-SUCCINAMATE
ω-AMI-DASE
NH3
2-OXO-GLUTARATE
ASPARTATE TRANSAMINASE
L-GLUTAMATE
SUCCINATE, 2-OXOGLUTARATE, MALEATE
ASPARTATE AMMONIA-LYASE
Co++
CITRATE
ATP
MALONATE, OXALO-ACETATE
FUMARATE
SUCCINATE DEHYDROGENASE
FADH2 · E
FAD · E
ACCEPTOR (UBIQUI-NONE)
ACC · H2 (UBIQUI-NOL)
S(= L)-MALATE
FUMARATE HYDRATASE (FUMARASE)
H2O
MALATE DEHYDROGENASE
NAD+
NADH + H+
MALATE SYNTHASE
PHOSPHO-ENOLPYRUVATE
SUCCINATE
CoA-SH
SUCCINYL-CoA-HYDROLASE
PPi, ATP
SUCCINYL-CoA-LIGASES
SUCCINYL-CoA
GTP(ITP)
GDP(IDP)
Pi
CO2
2 Cyl b-Fe++
2 H+
FORMATE DEHYDRO-GENASE (CYTOCHROME)
MOLYBDO-PTERIN
2 Cyb-Fe++
NADH + H+
FORMATE DEHYDRO-GENASE
NAD+
FORMYL-CoA
FORMYL-CoA HYDRO-LASE
FORMATE
H2O
CoA-SH
OXALATE DECARBOXY-LASE
CO2
OXALYL-CoA DECARBOXY-LASE
OXALATE-CoA-TRANSFERASE
Glyoxy-late cycle
FERRE-DOXIN (red)
FERRE-DOXIN (ox.)
2-OXO-GLUTARATE SYNTHASE
O2
FORMATE
(active) FORMATE ACETYLTRANSFERASE
higher ACYL-CoA, ATP, (2-OXO-GLUTARATE)
6-S-ACETYL-DIHYDROLIPOATE
DIHYDROLIPOAMIDE ACETYL-TRANS-FERASE
ACETYL-CoA
CITRATE SYNTHASE
CITRATE LYASE
Pi
ADP
ATP CITRATE LYASE
FRUCTOSE, GLYCEROL
Mg++
CoA-SH
ATP
DIHYDROLIPOAMIDE DEHYDRO-GENASE
NAD+
NADH + H+
CITRATE
CARNITINE ACETYLTRANSFERASE
CARNI-TINE
ACONITATE HYDRATASE (ACONITASE)
(+)ACETYL-CARNITINE
(−)O-ACETYL-CARNITINE
cis-ACONITATE
ACONITATE DECARBOXYLASE
CO2
ITACONATE
GLYCOLATE
GLYOXYLATE REDUCTASE
NAD+ NADH + H+
(S)-2-HYDROXY-ACID OXIDASE
FMN · E
FMNH2 · E
H2O2
O2
GLYOXYLATE
NH3
D-AMINO ACID OXIDASE
H2O
FAD
GLYCINE TRANSAMINASE
PyrP
L-GLUT-AMATE
FLUORO-CITRATE
ISOCITRATE LYASE
Mg++
MALATE, SUCCINATE, PHOSPHOENOL-PYRUVATE
threo-Ds-ISOCITRATE
A-3,5-MP (Note 25)
ISOCITRATE DEHYDRO-GENASE (NADP)
NADPH + H+
NADP+
OXALO-SUCCINATE
ISOCITRATE DEHYDRO-GENASE (NAD+)
NAD+
NADH + H+
CO2
(ATP), (NADH)
(AMP at low CITRATE), (ADP)
Citrate cycle
2-OXO-GLUTARATE
2-OXO-GLUTARAMATE
L-AMINO ACID
GLUTAMINE-OXOACID TRANSAMINASE
2-OXOACID
PyrP
ACETATE
ACETYL-CoA-LIGASE
Mg++
ATP
PPi
AMP
ACETYL ADENYLATE
CITRATE LYASE
ACETATE-CoA LIGASE
Mg++
CoA-SH
AMP
PROTEIN KINASE A(+ others?)
ADP
ATP
Mg++
P · inac-tive
H2O
[ACETYL-CoA CARBOXY-LASE] PHOS-PHATASE
Pi
PROTEINS
GLYCYL-tRNA
GLYCINE-tRNA LIGASE
ACETYL-CoA
GLYCINE
5-AMINOLEVULINATE SYNTHASE
increased in acute intermittent porphy
5-AMINO-LEVULINATE SYNTHASE
HEME
hν (in plants and photo-bacteria)
DIHYDRO-LIPOAMIDE SUCCINYL TRANS-FERASE
DIHYDRO-LIPO-AMIDE DEHY-DRO-GENASE
Deficient in hyper-oxaluria I
PYRUVATE
ALANINE-GLYOXYLATE TRANS-AMINASE
L-ALA-NINE
ACTH (via A-3,5-M
2-OXOGLU-TARATE DECARBOXYLASE
2-OXOGLUTARATE DEHYDROGENASE SYSTEM
MALATE DEHYDROGENASE
NADH + H+
NAD+
ACCEPTOR · H2
ACCEPTOR
2-HYDROXYGLUTAR DEHYDROGENASE
NADPH + H+/NA
GLUTAMATE DEHYDRO [Note 14 (
CORTI-SONE
OXALO-ACETATE
NADPH + H+
NADP
GLUTAMATE SYNTHASE (NADPH)

Clotting Cascade

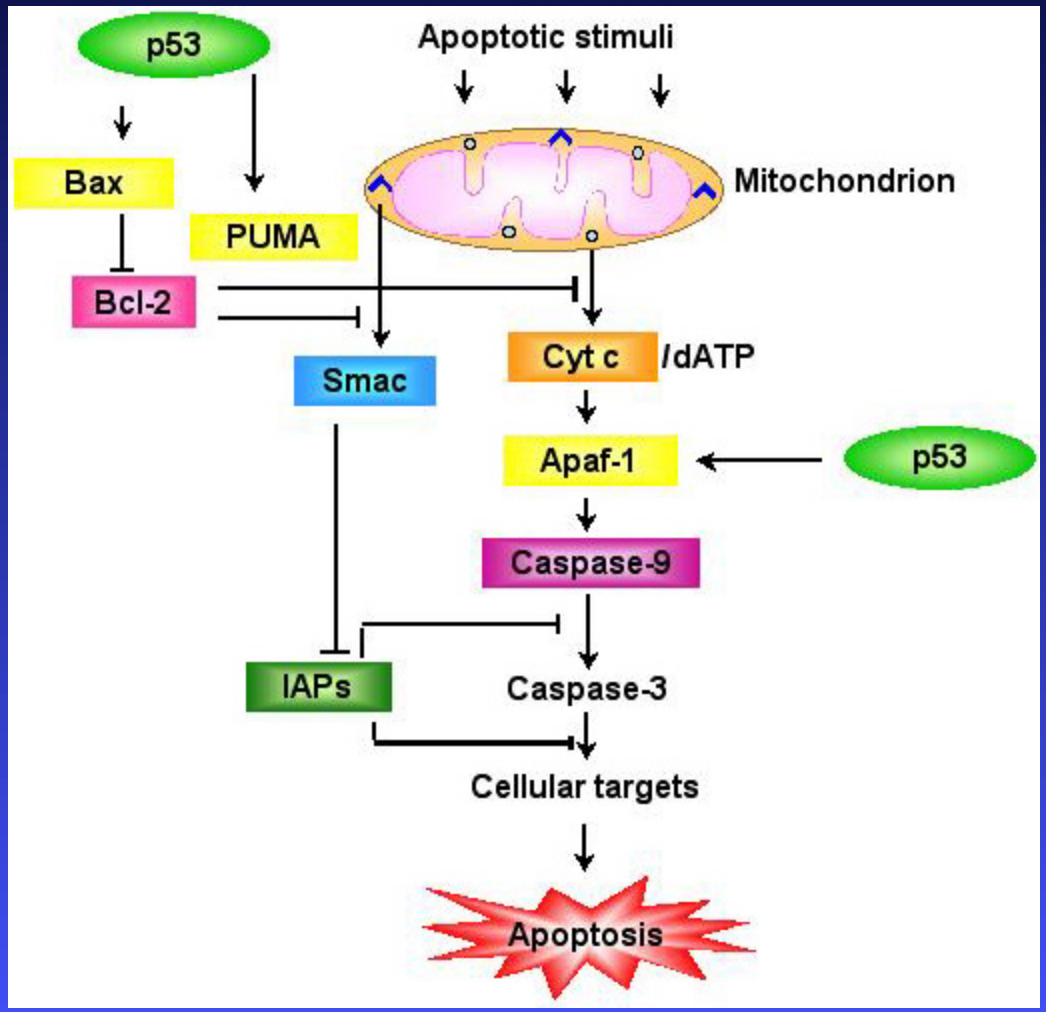


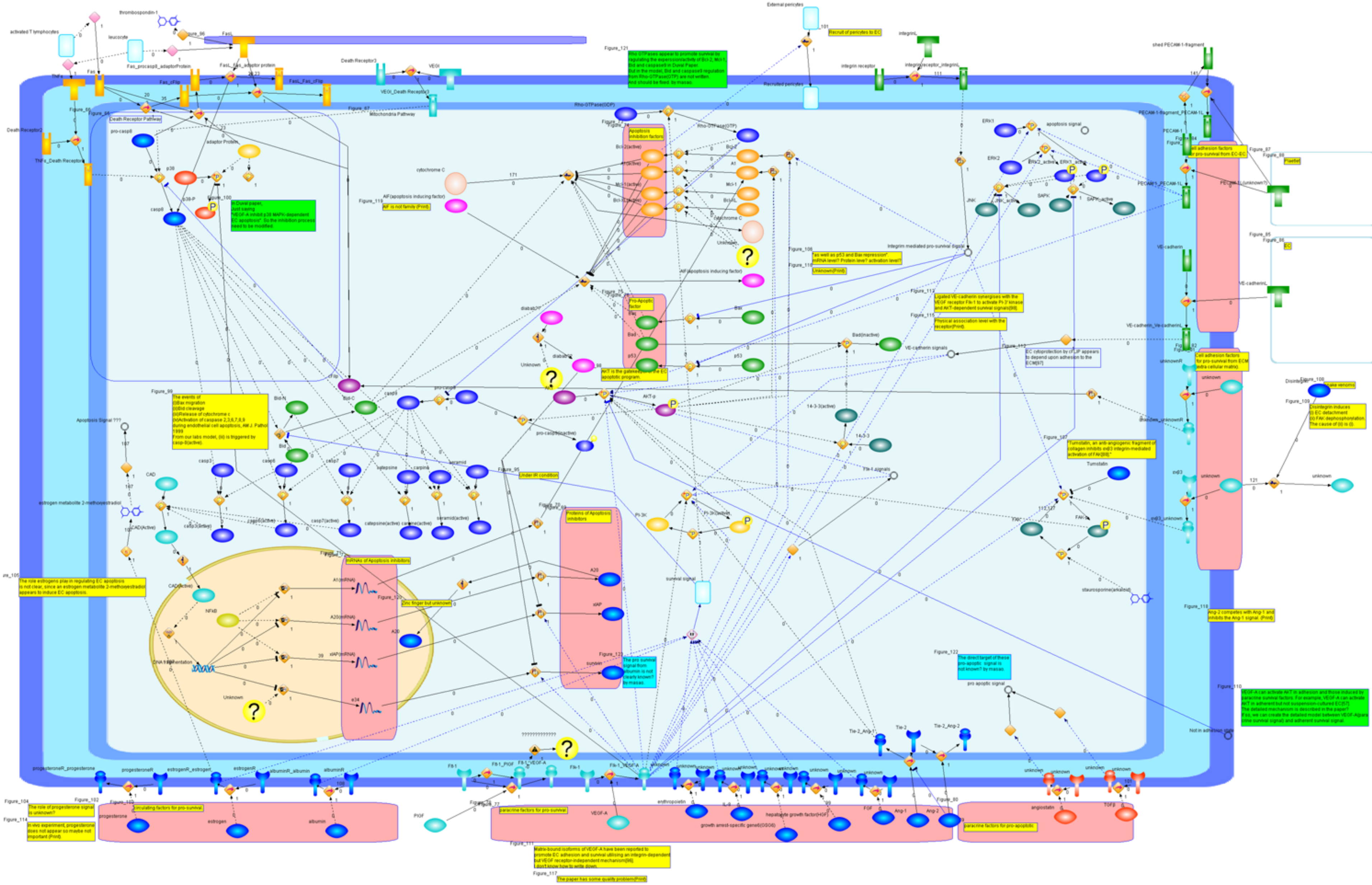
Clotting Cascade




SABiosciences
www.SABiosciences.com
www.ProteinLounge.com
IFNα
IFNβ
IFNγ
Macrophage
IL-1
IL-6
IL-10
IL-12
IL-15
TNFα
IL-10
IL-12
TNFα
TNFβ
IL-1
IFNα
IFNβ
TNFα
TNFβ
IL-1 IFNα
IL-6 IFNγ
IL-8 IFNα
IL-10
IL-12
IL-15
IL-18
IL-1
IL-8
TNFα
TNFα
IL-1 IFNα
IL-3 IFNβ
IL-4 IFNγ
IL-10 TNFα
IL-13 TNFβ
IL-1
IL-8
IL-5
B-Cell
Neutrophil
Eosinophil
IL-1 IFNα
IL-6 IFNβ
IL-10 TNFα
IL-12 TNFβ
TNFα
IL-1 IFNα
IL-2 IFNβ
IL-4 IFNγ
IL-6
IL-10
IL-13
IL-14
IL-1 IFNγ
IL-3 TNFα
IL-4 TNFβ
IL-8
Basophil
T-Cell
IL-4
IL-4
IL-1
IL-3
IL-4
IL-8
IL-2 IL-15
IL-4 IL-17
IL-6 IFNα
IL-8 IFNβ
IL-9 IFNγ
IL-10
IL-4
IL-3
IL-9
IL-10
IL-4
IL-3
IL-4
IL-5
IL-4
IL-4
IL-5
IL-10
Mast Cell

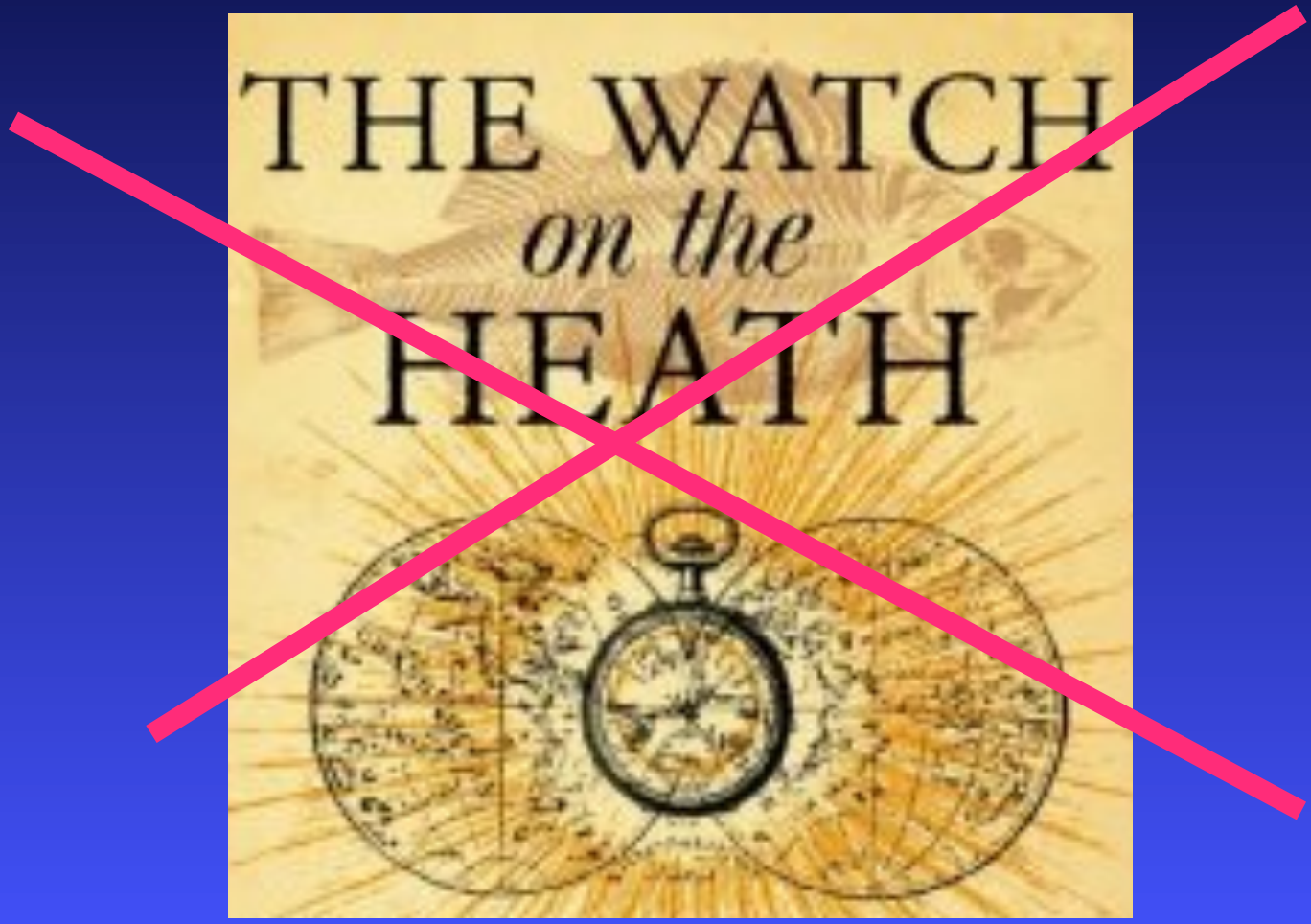
Apoptosis


p53
Apoptotic stimuli
Bax
Mitochondrion
PUMA
Bcl-2
Cyt c
/dATP
Smac
Apaf-1
p53
Caspase-9
IAPs
Caspase-3
Cellular targets
Apoptosis



Death Receptor Pathway
Mitochondria Pathway
In Duval paper, Just saying "VEGF-A inhibit p38 MAPK-dependent EC apoptosis". So the inhibition process need to be modified.
Rho GTPases appear to promote survival by regulating the experssion/activity of Bcl-2, Mcl-1, Bid and caspase9 in Duval Paper. But in the model, Bid and caspase9 regulation from Rho-GTPase(GTP) are not written. And should be fixed. by masao.
Recruit of pericytes to EC
Apoptosis inhibition factors
AIF is not family (Print)
"as well as p53 and Bax repression". mRNA level? Protein leve? activation level?
Unknown(Print)
Pro-Apoptic factor
AKT is the gatekeeper of the EC apoptotic program.
Ligated VE-cadherin synergises with the VEGF receptor Flk-1 to activate PI-3' kinase and AKT-dependent survival signals[98].
Physical association level with the receptor(Print).
EC cytoprotection by cFLIP appears to depend upon adhesion to the ECM[97]
Cell adhesion factors for pro-survival from EC-EC
Cell adhesion factors for pro-survival from ECM extra cellular matrix).
Platelet
EC
Snake venoms
Disintegrin induces (i) EC detachment (ii) FAK dephosphorylation. The cause of (ii) is (i).
The events of (i)Bax migration (ii)Bid cleavage (iii)Release of cytochrome c (iv)Activation of caspase 2,3,6,7,8,9 during endothelial cell apoptosis, AM J. Pathol 1999 From our labs model, (iii) is triggered by casp-8(active).
Under IR condition
"Tumstatin, an anti-angiogenic fragment of collagen inhibits αvβ3 integrin-mediated activation of FAK[88]."
Proteins of Apoptosis inhibitors
mRNAs of Apoptosis inhibitors
Zinc finger but unknown
The role estrogens play in regulating EC apoptosis is not clear, since an estrogen metabolite 2-methoxyestradiol appears to induce EC apoptosis.
The pro survival signal from albumin is not clearly known? by masao.
The direct target of these pro-apoptic signal is not known? by masao.
Ang-2 competes with Ang-1 and inhibits the Ang-1 signal. (Print)
VEGF-A can activate AKT in adhesion and those induced by paracrine survival factors. For example, VEGF-A can activate AKT in adherent but not suspension-cultured EC[57]. The detailed mechanism is described in the paper? If so, we can create the detailed model between VEGF-A(paracrine survival signal) and adherent survival signal.
The role of progesterone signal is unknown?
In vivo experiment, progesterone does not appear so maybe not important (Print).
circulating factors for pro-survival
paracrine factors for pro-survival
paracrine factors for pro-apoptotic
Matrix-bound isoforms of VEGF-A have been reported to promote EC adhesion and survival utilising an integrin-dependent but VEGF receptor-independent mechanism[96]. I don't know how to write down.
The paper has some quality problem(Print)

The body is not like a watch



The Body is a Tangled Bank

Organically complex mechanisms are very different from components of machines