Environmental Health Very Short Course

Environment – Health Continuum
STEM Foundations and Connections

with David Petering
Director, NIEHS Children's Environmental Health Sciences Core Center
University Distinguished Professor of Chemistry and Biochemistry

Short Course Topics

Introduction to environmental health

Introductory framework: organism and the environment

Examples of environmental adaptation: interconnectedness of life

Implications for the environment and human health of the discovery and domestication of fossil hydrocarbons

Key concepts in environmental health:

- multiple exposures-mixtures
- vulnerable populations-children
- role of the built environment
- multiple confounding factors-causal relationships

Public Health and Environmental Health

Former President, Medical College of Wisconsin, Michael Bolger

There are four things that determine your health:

- Your parents genetics
- Your personal habits (smoking, alcohol, etc.)
- *Your environment*
- Your health care system, which contributes at 5% to your health and costs $1.5-2 trillion dollars per year in the USA

UWM School of Public Health

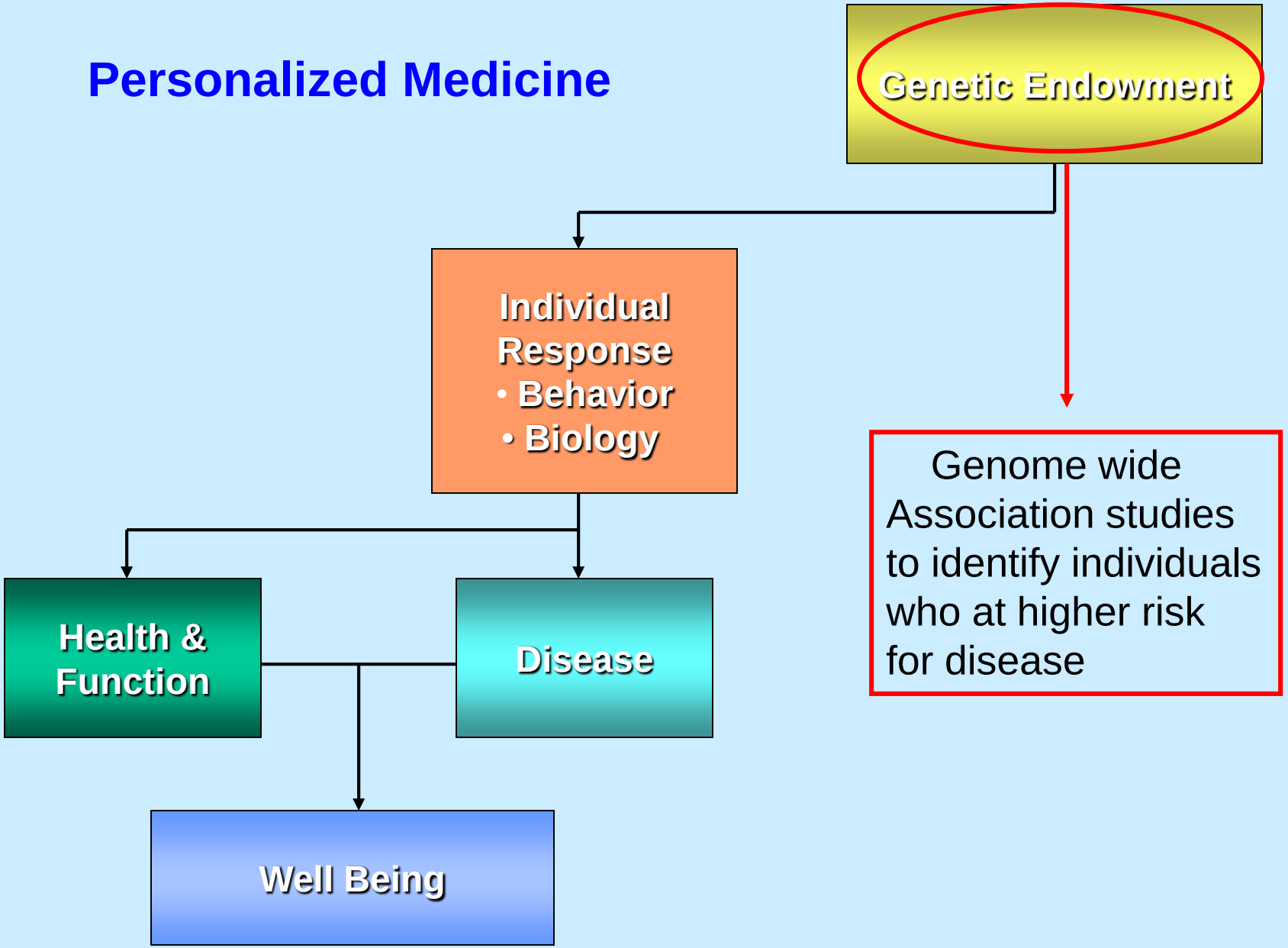
Environmental and Occupational Health
Epidemiology
Community and Behavioral Health
Health Administration and Policy

Characteristics

Interdisciplinary: natural and social sciences
Population based
Focus: physical and social health well-being of populations

Science and Society

Personalized Medicine



Adapted from Evans, R. G., & Stoddart, G. L. (1990). Producing health, consuming health care. *Social Science and Medicine, 31,* 1347-1363.

Genome-Wide Association Studies

Genomic DNA base sequence-$5x10^9$ bases

↓

Hypothesis: gene variations cause disease

↓

Identify DNA variants associated with diseases
Assumption-diseases are common; so are variants
e.g. SNPs-single nucleotide polymorphisms

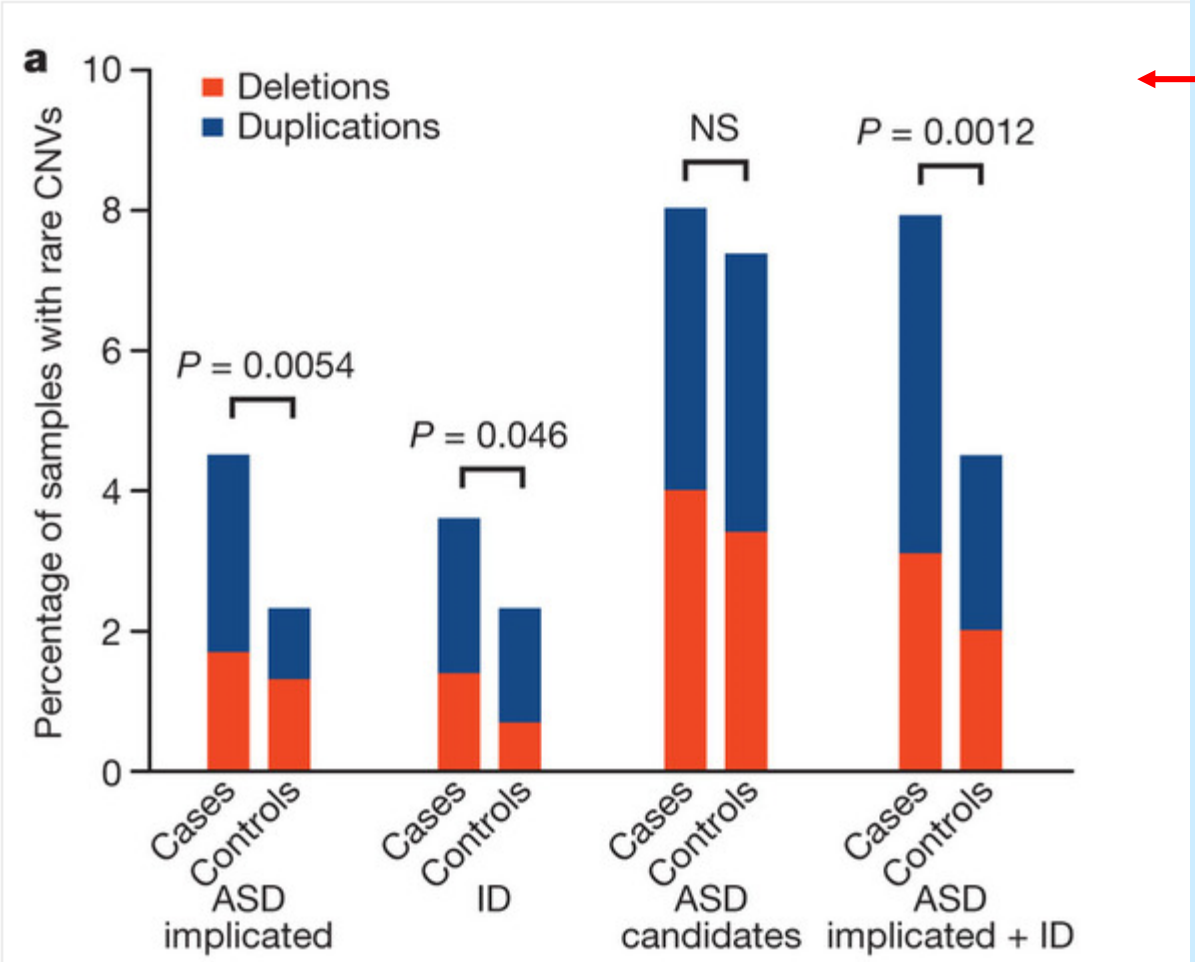
Researchers ID certain genes tied to autism

By Mark Johnson of the Journal Sentinel

Posted: June 9, 2010 | (3) COMMENTS

An international team of researchers unveiled the most detailed picture yet of the genetic causes of autism, identifying specific genes and pathways that play a role in the complex disorder, and that can now be targeted by drug companies hoping to provide treatment for millions worldwide.

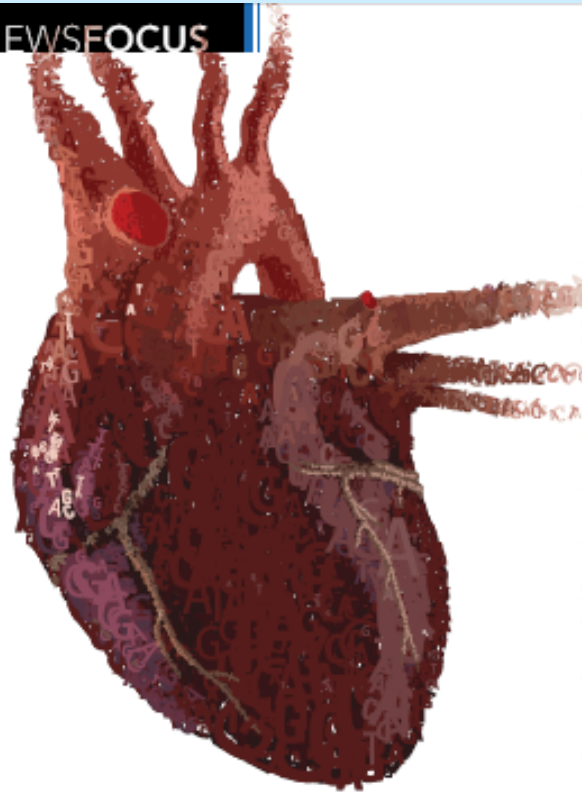
Figure 2: CNV burden in known ASD and/or intellectual disability genes.



CNV: copy number variant;
ASD: autism spectrum disease;
ID: intellectual disability
D Pinto *et al. Nature* **000**, 1-5 (2010)
doi:10.1038/nature09146

"Boys are 4 times more likely to develop autism than girls…girls with autism had more of the rare duplications and deletions than boys and the events in girls also involved more genes-implying, perhaps, that girls require a higher number of genetic changes to develop the disorder."
S. Roan, Milw. Journal-Sent 6/9/11

Genetic Contribution to Major Diseases



Major Heart Disease Genes Prove Elusive

So far, genome-wide association studies have not found common genes with a big impact on heart health; researchers hope that the low-effect genes they are finding will help identify pathways and drug targets

THE EXCITEMENT BEGAN 5 YEARS AGO, when a study of 146 Caucasian volunteers turned up a common gene variant among those with the eye disease macular degeneration. Researchers had used a new strategy: They scanned large stretches of the genomes of the sick and the healthy and found a single DNA base that was much more likely to be present in those whose eyes were failing.

The finding was remarkable: Relatively few people participated in the study, yet those with two copies of the suspect gene variant had 10 times the risk of macular degeneration, a huge increase. Furthermore, the method the group used, called genome-wide association (GWA), had some big advantages: It was unbiased, testing thousands of gene-disease associations at once, not just a researcher's favorites. And it pointed to common variants, found in at least 5% of individuals studied. GWA studies offered hope of identifying people at risk for diseases, uncovering new disease mechanisms, and finding new targets for therapy.

Almost immediately, researchers applied GWA to other conditions. But they were quickly stymied. "People did studies with 300 or 500 people and didn't find anything, then did 1000 and didn't find anything," says Deepak Srivastava, who directs the Gladstone Institute of Cardiovascular Disease at the University of California (UC), San Francisco. It quickly became clear that macular degeneration was an exception. Most GWA studies needed 10,000 or more volunteers to get a statistically significant result, because the effect of each gene was so small.

Since the human genome was sequenced 10 years ago, technology has moved with lightning speed; many now believe that GWA methods, which cover a fraction of the genome, are becoming obsolete. Sequencing costs continue to plunge, and within a few years sequencing entire genomes of hundreds of subjects will be financially feasible.

What has the GWA experience taught us? The results from one group of GWA studies, for heart disease, are typical, with a mixed record and an uncertain legacy. The technique has identified dozens of variants, but all have weak effects; so far, almost none has led to DNA changes that actually cause disease. Researchers have had more success finding variants that link to tightly defined conditions like high cholesterol than to heart failure, a catch-all disease.

"At the end of the day, we have a bunch of loci and genes, but none of them" do all that much to raise the risk of heart disease, says Eric Topol, a cardiologist and director of the Scripps Translational Science Institute in San Diego, California. Nor have they yet altered our understanding of how the heart falters—knowledge, Topol says, that will take time to develop.

GWA studies still have many backers. "We have new technology that's enabled us to look at things we've never seen before," says Bruce Psaty, a cardiovascular disease epidemiologist at the University of Washington (UW) School of Medicine in Seattle. And Francis Collins, director of the National Institutes of Health (NIH), has said that the approach has provided "1000 new drug targets" (*Science*, 28 May, p. 1090).

Clues missing

The first GWA results for heart disease hit in 2007. Three studies examined coronary artery disease, in which plaque builds up in the arteries and narrows them. Together with subsequent studies, they identified 12 new genetic variants, called single-

Genetic Contribution to Major Diseases

The authors conclude that although GWA studies have identified several genetic loci, particularly for breast, prostate and colon cancer, "the explanatory power of these loci to predict individual cancer risk is limited. . .." In other words, the average level of risk for associations identified by GWA studies, although statistically significant, is relatively small, even though other factors may increase the risk for any particular individual. Furthermore, they write: "Performing GWA studies using all currently available samples on common cancers would yield many more genetic loci, but almost all of them would also have small or very small effects."

J. Ioannidis, J. Natl. Cancer Institute, 102, May, 28, 2010

Rare variant hypothesis: many rare genetic changes account for overall risk

-Does this provide pathway to reduce incidence or severity of disease?

Experience with orphan diseases (rare *genetic* diseases)

Genetic Contribution to Major Diseases

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What is missing here?

Genetic Contribution to Major Diseases

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J. Ioannidis, J. Natl. Cancer Institute, 102, May, 28, 2010

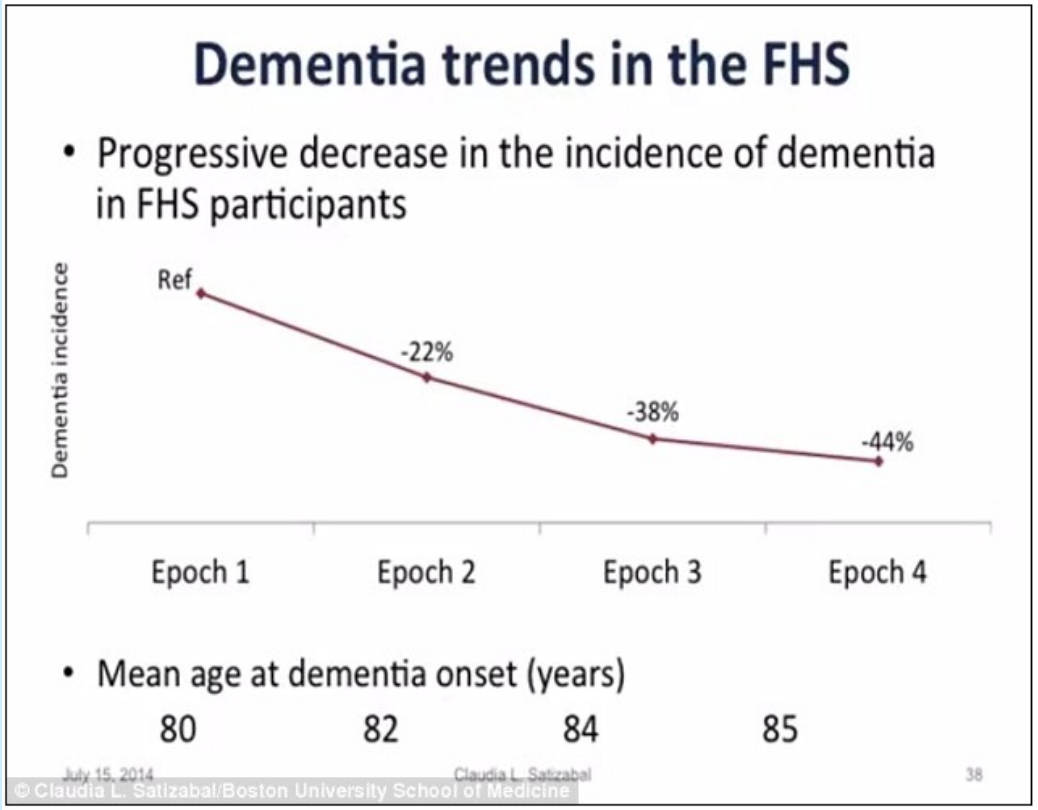
President's Cancer Panel, 2009

Re autism DNA modifications:
"The obvious conclusion one has to reach is that some environmental exposures may be playing a role."
S. Roan, Milw. Journal Sentinel, 6/9/11

Neuropathology and Applied Neurobiology (2014), **40**, 97–105

Review: The genetics of Alzheimer's disease; putting flesh on the bones

"A recent meta-analysis by the International Genomics of Alzheimer's Project (IGAP) reported 11 new Alzheimer's susceptibility loci (*CASS4*, *CELF1*, *FERMT2*, *HLA-DRB5/HLA-DRB1*, *INPP5D*, *MEF2C*, *NME8*, *PTK2B*, *SLC24A4/RIN3*, *SORL1* and *ZCWPW1*), and confirmed eight (*CR1, BIN1, CD2AP, EPHA1, CLU, MS4A6A, PICALM* and *ABCA7*) of the nine previously reported genome-wide associations in addition to *APOE* [1]; the exception being *CD33* which failed to replicate. Consequently genetic discoveries within the last 5 years account for ~47% of the population attributable risk (PAR) of LOAD (late-onset AD).



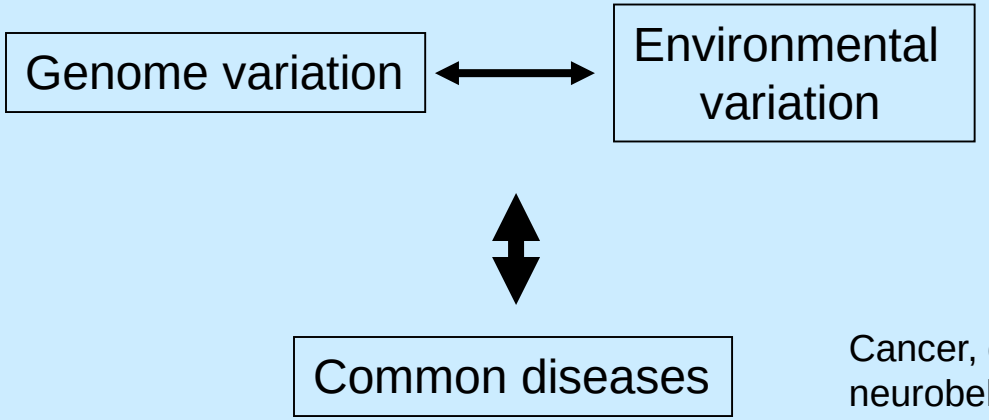
Decline: The federally funded Framingham study, pictured, tracked new dementia cases among several thousand people 60 and older in five-year periods starting in 1978, 1989, 1996 and 2006 and noted a decline

http://www.dailymail.co.uk/news/article-2692975/US-rate-Alzheimers-disease-DECLINING.html

Speculation: decline due to education and reduction in risk factors such as heart disease and stroke

Genomic Analysis Leads to Few Solutions

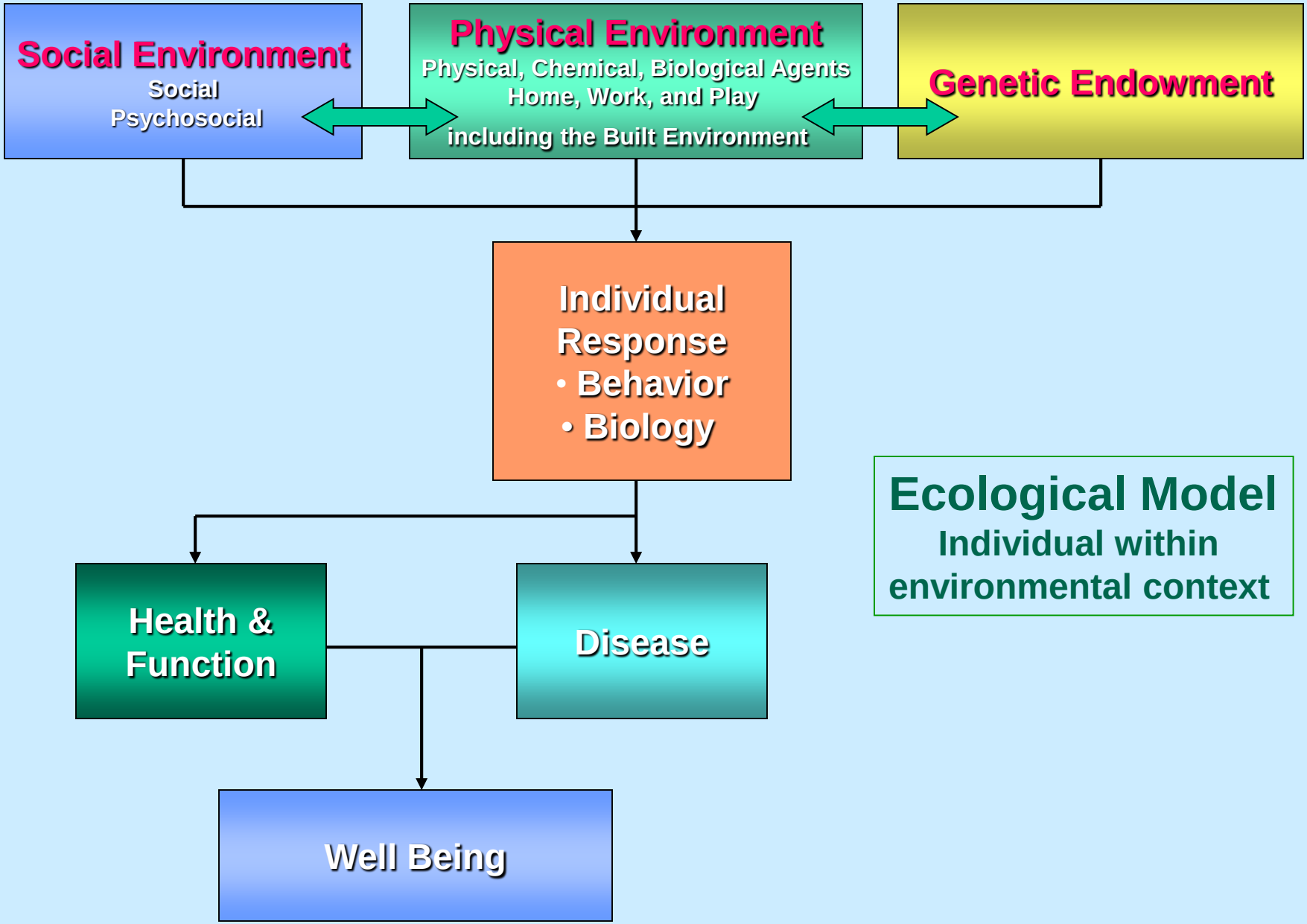
Alternative hypothesis: genome loads the gun; environment pulls the trigger
Kenneth Olden, former Director National Institute of Environmental Health Science



Cancer, cardiovascular disease, neurobehavioral disease, etc.

Genetic effects of toxic and essential elements in humans: arsenic, cadmium, copper, lead, mercury, selenium, and zinc in erythrocytes, Whitfield et al, Environmental Health Perspectives, 118,776 (2010): "Although environmental exposure is a precondition for accumulation of toxic elements, individual characteristics and genetic factors are also important."

Whatever substantial genomic impact that may exist will only reveal itself in relation to the environment!



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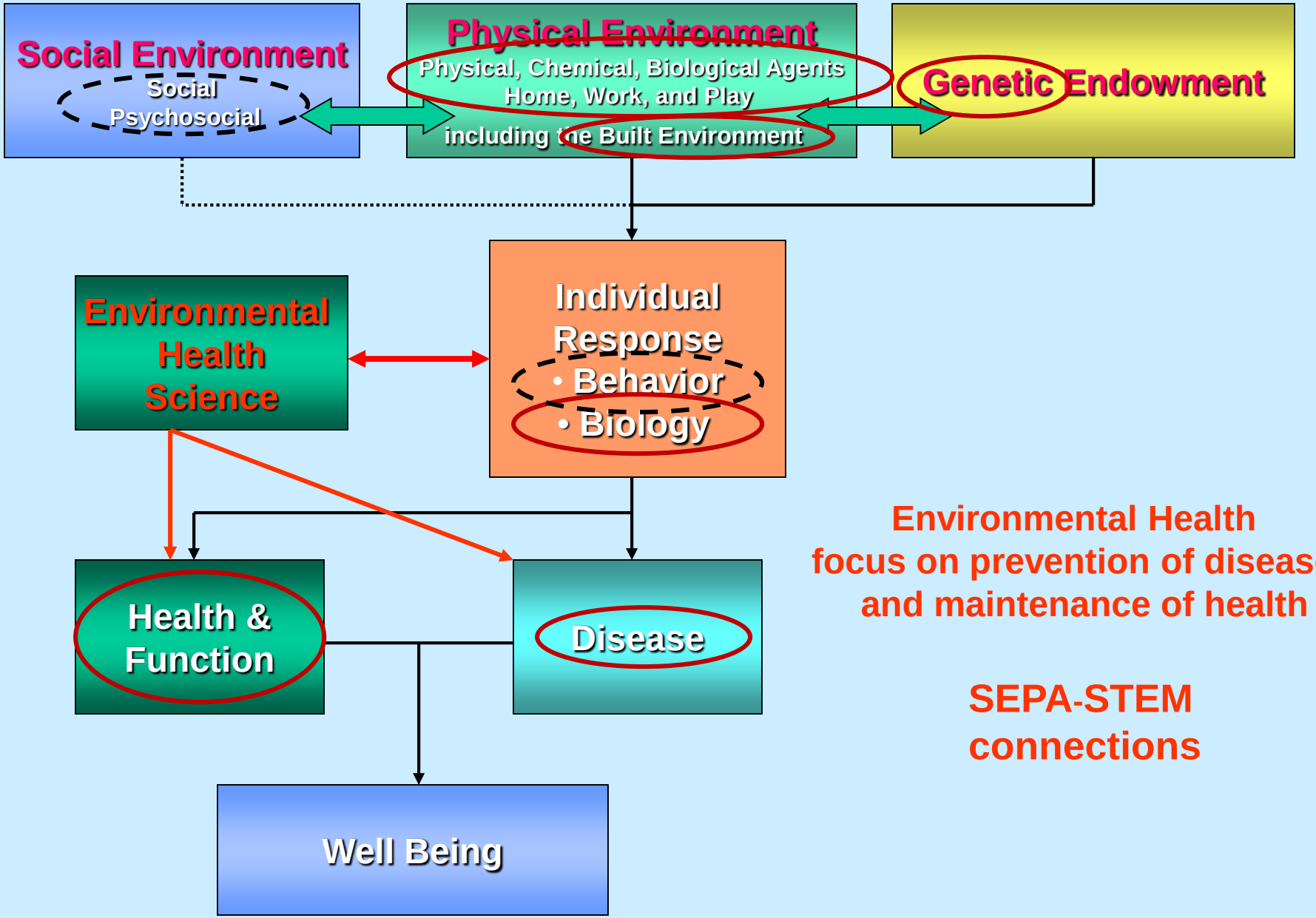


Environmental Health focus on prevention of disease and maintenance of health

SEPA-STEM connections

Centers for Disease Control: Fact Sheet
Actual Causes of Death in the United States, 2000

Leading Causes of Death

Heart disease	30%
Cancer	20%
Stroke	7%
Chronic respiratory Disease	5%
Injuries	4%
Diabetes	3%
Pneumonia/influenza	3%
Alzheimers disease	2%
Kidney disease	2%

Centers for Disease Control: Fact Sheet
Actual Causes of Death in the United States, 2000

Leading Causes of Death		Actual Causes of Death	
Heart disease	30%	Tobacco	17%
Cancer	20%	Diet/physical inactivity	15%
Stroke	7%	Alcohol	4%
Chronic respiratory Disease	5%	Infectious agents	4%
Injuries	4%	Toxic agents	3%
Diabetes	3%	Motor vehicles	2%
Pneumonia/influenza	3%	Firearms	1%
Alzheimers disease	2%	Sexual behavior	1%
Kidney disease	2%	Drug use	1%

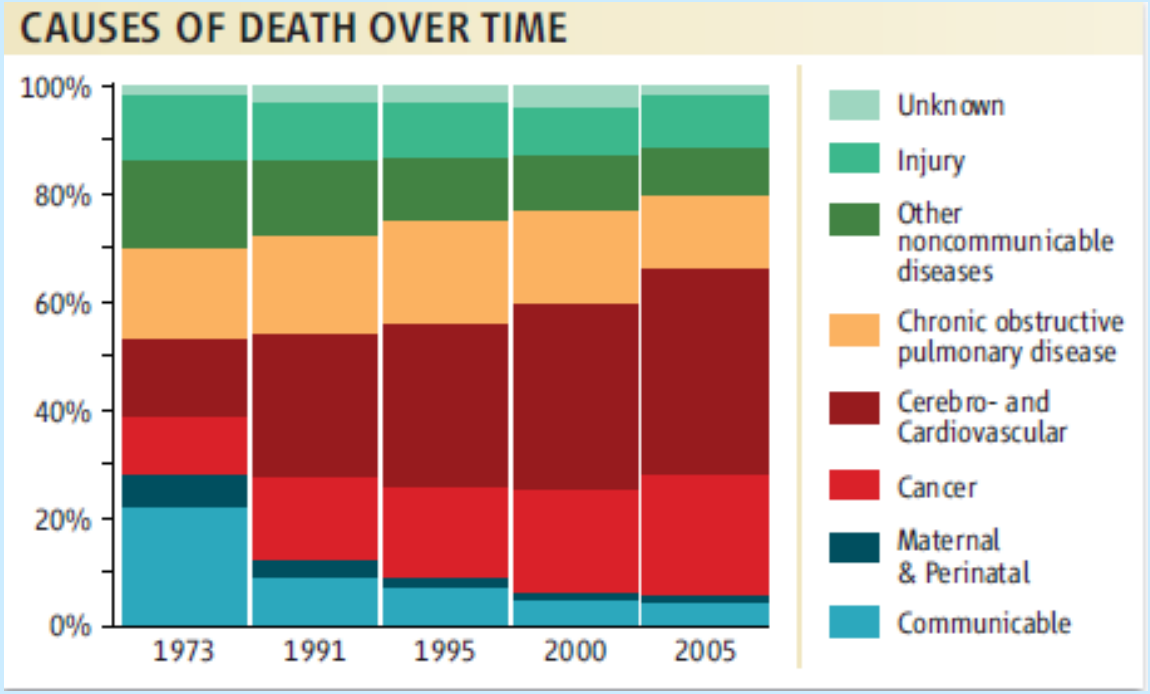
Science Magazine: China Confronts Ailments of Affluence
Third World-First World Diseases
Science, 328, 422 (2010)

PUBLIC HEALTH

A Sense of Crisis as China Confronts Ailments of Affluence

Science Magazine: China Confronts Ailments of Affluence Third World-First World Diseases

Science, 328, 422 (2010)



Science Magazine: China Confronts Ailments of Affluence
Third World-First World Diseases
Science, 328, 422 (2010)

Fat busters. Schools are turning to physical education to counter rising rates of childhood obesity.

China's growing affluence is driving sharp increases in what were once considered scourges of the Western world: lung and breast cancer, obesity, diabetes, hypertension, and cerebro- and cardiovascular diseases. A rapidly changing lifestyle appears to be to blame, as Chinese are smoking more; consuming more fat, sugar, salt, and refined grains; and leading increasingly sedentary lives, particularly in cities and booming coastal regions.

Growing affluence is fueled by…

China and the Burning of Coal

New coal-fired power plant every week.

- -Air pollution (SO_x, particulates, etc.) and respiratory disease
- -Acid rain and leaching of soil nutrients
- -Release of toxic agents (Hg)
- -CO_2 and energy production
- -Energy to drive an *early stage* industrial economy

Pudong region of Shanghai

Health and Disease – Then as Now

Hippocrates: "Disease is not caused by demons or capricious deities but rather by natural forces that obey natural laws.

The well-being of man is under the influence of the environment, including in particular air, water, places, and the various regimens. The understanding of the effect of the environment on man is the fundamental basis of the physician's art.

Health is the expression of a harmonious balance between the various components of man's nature and the environment and ways of life."

Man Adapting – Rene Dubos

Subduing infectious disease in the 17th and 18th centuries resulted from improvements in sanitation not miracle antibiotics.

Matters of Life and Death: Perspectives on Public health, Molecular Biology, Cancer and the Prospects for the Human Race, John Cairns

Most of our increase in life span is due to better "hygiene" or public health - clean air and water, stable sources of nutritious food, adequate shelter, good *biological* and *chemical hygiene*, etc. In a word, facets of (public) environmental health.

STEM subject matter

Beyond Mortality: Health Determinants: World Health Organization

Chemicals and Pathogens

Food and agriculture

Diet
Food biological and chemical contamination
Food toxins
Occupational hazards and accidents
Water quality

Water

Water quality: pathogens, chemicals

Energy

Fossil fuels and air pollution
Nuclear power
Accidents
Indoor pollution

Industry

Occupational chemical exposure
Environmental chemical exposure-waste disposal

Built environment

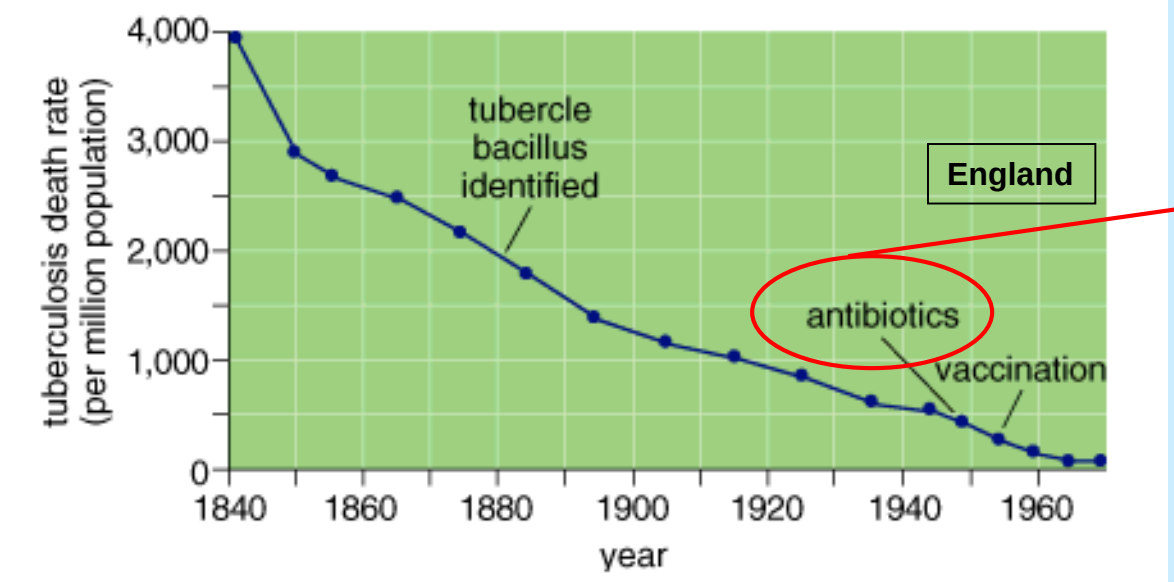
Housing-paint, vermin
Garbage disposal
Noise
Diet and physical activity

International

Long range air pollution
Hazardous materials transport
Ozone depletion
Climate change
Ocean pollution
Biodiversity loss

Environmental Health

- A society's health is dependent upon the quality of its physical, biological, chemical, and social-economic environment
- Societies that attend to the quality of the environment gain disproportionately in health in relation to their investment in health and well being



Clyde Herzman, "Health and Human Society," American Scientist, 89, 538 (2001).

Biological hygiene

Chemical Hygiene

2009

Fourth National Report on Human Exposure to Environmental Chemicals

Executive Summary

Department of Health and Human Services
Centers for Disease Control and Prevention
National Center for Environmental Health

www.ewg.org

10 random specimens of cord blood

Environmental Working Group; 2004

Body burden: the pollution in newborns

- Tested for 413 chemicals
- 287 chemicals detected; 200 average
- Carcinogens,
- Developmental toxicants
  - Birth weight
  - Birth defects
  - Impaired neurodevelopment, etc.
- Impacts of this mixture unstudied and unknown

Urinary Dimethylarsinic Acid

Metabolite of Arsenic

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

	Survey years	Geometric mean (95% conf. Interval)	Selected percentiles (95% confidence Interval) 50th	75th	90th	95th	Sample size
Total	03-04	**3.71** (3.33-4.14)	**3.90** (3.00-4.00)	**6.00** (5.00-7.00)	**11.0** (9.20-12.0)	**16.0** (13.0-17.8)	2568
Age group							
6-11 years	03-04	**3.73** (3.12-4.45)	**4.00** (3.00-4.00)	**6.00** (5.00-7.00)	**9.00** (7.00-12.0)	**12.0** (8.00-22.0)	292
12-19 years	03-04	**3.85** (3.34-4.42)	**4.00** (3.00-4.00)	**6.00** (5.00-7.10)	**9.30** (7.70-12.0)	**13.0** (10.0-16.0)	728
20 years and older	03-04	**3.69** (3.31-4.11)	**3.70** (3.00-4.00)	**6.00** (5.00-7.00)	**11.0** (10.0-12.0)	**16.0** (13.0-19.0)	1548
Gender							
Males	03-04	**4.12** (3.60-4.71)	**4.00** (3.70-4.30)	**6.00** (5.60-7.70)	**11.0** (9.00-15.0)	**17.0** (12.1-22.0)	1284
Females	03-04	**3.37** (3.00-3.78)	**3.00** (3.00-4.00)	**5.50** (4.80-6.20)	**10.0** (8.00-11.0)	**14.0** (11.0-17.7)	1284
Race/ethnicity							
Mexican Americans	03-04	**4.72** (4.27-5.22)	**4.80** (4.00-5.00)	**7.00** (6.00-9.00)	**12.0** (10.0-16.0)	**17.0** (12.0-25.0)	621
Non-Hispanic blacks	03-04	**4.27** (3.71-4.92)	**4.00** (3.50-5.00)	**7.00** (6.00-8.00)	**11.6** (9.00-15.0)	**16.0** (14.0-18.7)	725
Non-Hispanic whites	03-04	**3.27** (2.95-3.62)	**3.00** (3.00-3.80)	**5.00** (4.60-6.00)	**9.00** (7.00-10.0)	**12.0** (9.50-15.0)	1078

Limit of detection (LOD, see Data Analysis section) for Survey year 03-04 is 1.7.

CDC 4th Report on Chemical Exposure

New Chemicals in the *Fourth Report*

Acrylamide
Acrylamide hemoglobin adducts
Glycidamide hemoglobin adducts

50%, 700x LOD → **Perchlorate**

Total and Speciated Arsenic
Arsenic, Total
Arsenic (V) acid
Arsenobetaine
Arsenocholine
Arsenous (III) acid
Dimethylarsinic acid
Monomethylarsonic acid
Trimethylarsine oxide

50%, 7x LOD → Lead (1-5 y)
25%, 8x LOD → Mercury
50%, 2.5x LOD →

Environmental Phenols
Benzophenone-3 (2-Hydroxy-4-methoxybenzophenone)
Bisphenol A (2,2-*bis* [4-Hydroxyphenyl] propane)
4-*tert* -Octylphenol (4-[1,1,3,3-Tetramethylbutyl] phenol)
Triclosan (2,4,4'-Trichloro-2'-hydroxyphenyl ether)

Phthalate Metabolite
Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)

Perfluorochemicals
Perfluorobutane sulfonic acid (PFBuS)
Perfluorodecanoic acid (PFDeA)
Perfluorododecanoic acid (PFDoA)
Perfluoroheptanoic acid (PFHpA)
Perfluorohexane sulfonic acid (PFHxS)
Perfluorononanoic acid (PFNA)
Perfluorooctane sulfonamide (PFOSA)
Perfluorooctane sulfonic acid (PFOS)
2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH)
2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH)
Perfluorooctanoic acid (PFOA)
Perfluoroundecanoic acid (PFUA)

50%, 50x LOD →

Non-Dioxin-Like Polychlorinated Biphenyls
2,2',3,5'-Tetrachlorobiphenyl (PCB 44)
2,2',4,5'-Tetrachlorobiphenyl (PCB 49)
2,2',3,3',4,4',5,5',6,6'-Decachlorobiphenyl (PCB 209)

25%, 4x LOD →

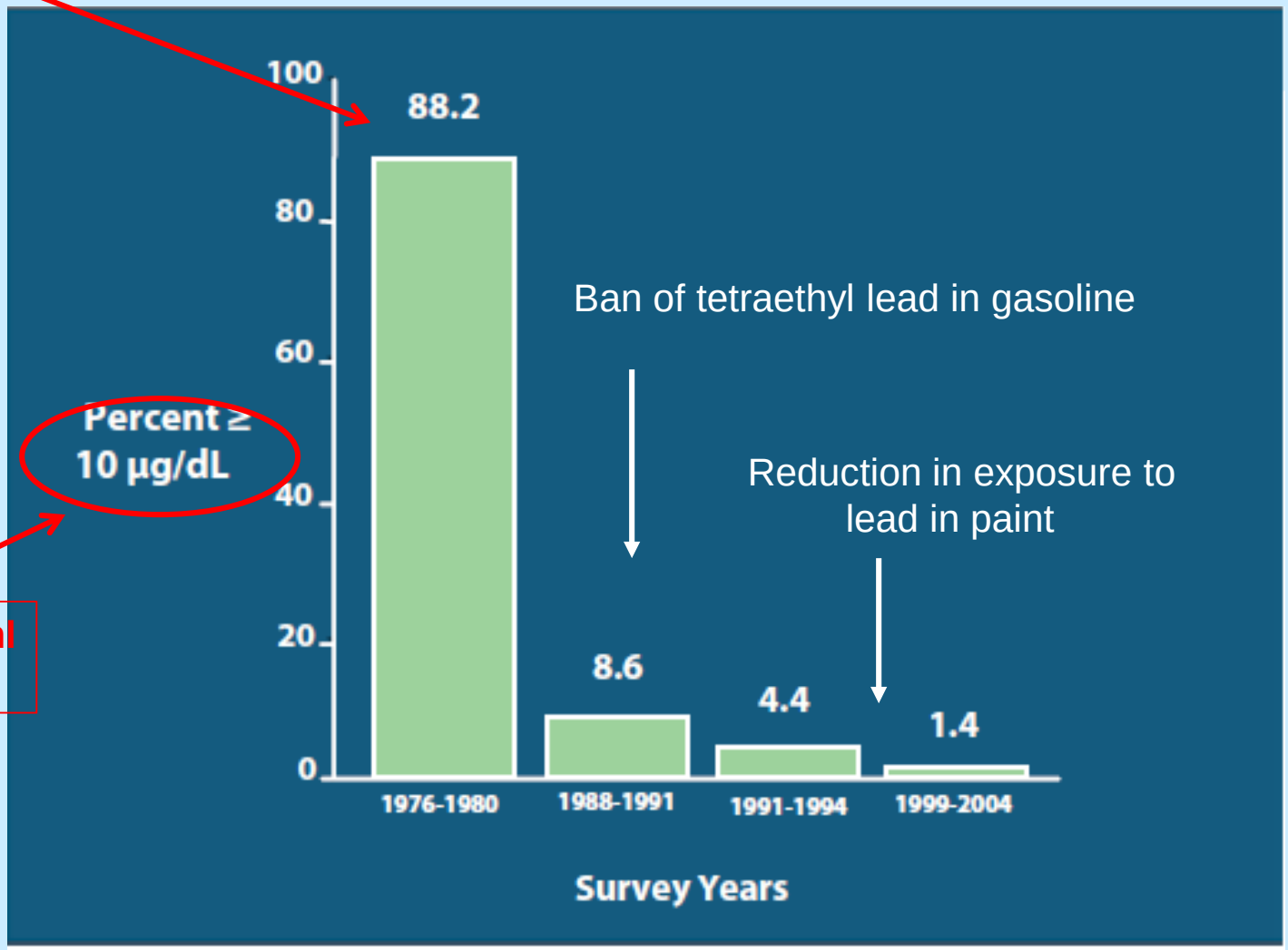
Brominated Fire Retardants
2,2',4-Tribromodiphenyl ether (BDE 17)
2,4,4'-Tribromodiphenyl ether (BDE 28)
2,2',4,4'-Tetrabromodiphenyl ether (BDE 47)
2,3',4,4'-Tetrabromodiphenyl ether (BDE 66)
2,2',3,4,4'-Pentabromodiphenyl ether (BDE 85)
2,2',4,4',5-Pentabromodiphenyl ether (BDE 99)
2,2',4,4',6-Pentabromodiphenyl ether (BDE 100)
2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE 153) ← 25%, 5x LOD
2,2',4,4',5,6'-Hexabromodiphenyl ether (BDE 154)
2,2',3,4,4',5',6-Heptabromodiphenyl ether (BDE 183)
2,2',4,4',5,5'-Hexabromobiphenyl (BB 153)

Disinfection By-Products (Trihalomethanes)
Bromodichloromethane ← 25%, 6x LOD
Dibromochloromethane (Chlorodibromomethane)
Tribromomethane (Bromoform)
Trichloromethane (Chloroform)

Volatile Organic Compounds
Benzene ← 25%, 2-4X LOD
Chlorobenzene (Monochlorobenzene)
1,2-Dibromo-3-chloropropane (DBCP)
Dibromomethane
1,2-Dichlorobenzene (*ortho*-Dichlorobenzene)
1,3-Dichlorobenzene (*meta*-Dichlorobenzene)
1,4-Dichlorobenzene (*para*-Dichlorobenzene)
1,1-Dichloroethane
1,2-Dichloroethane (Ethylene dichloride)
1,1-Dichloroethene (Vinylidene chloride)
cis-1,2-Dichloroethene
trans-1,2-Dichloroethene
Dichloromethane (Methylene chloride)
1,2-Dichloropropane
2,5-Dimethylfuran (DMF)
Ethylbenzene
Hexachloroethane
Methyl *tert*-butyl ether (MTBE) ← 50%, 100x LOD
Nitrobenzene
Styrene ← 25%, 3x LOD
1,1,2,2-Tetrachloroethane
Tetrachloroethene (Perchloroethylene)
Tetrachloromethane (Carbon tetrachloride)
Toluene
1,1,1-Trichloroethane (Methyl chloroform)
1,1,2-Trichloroethane
Trichloroethene (Trichloroethylene, TCE) ← 100%, <LOD
meta- and *para*-Xylene
ortho-Xylene

Chemical Hygiene

40 µg/100 ml



5 µg/100 ml
0.05 ppm

Figure 1. Percentage of children 1-5 years old in the U.S. population with elevated blood lead levels (≥ 10 µg/dL).[1]

[1] Jones RL, Homa DM, Meyer PA, Brody DJ, Caldwell KL, Pirkle JL, Brown MJ. Trends in blood lead levels and blood lead testing among U.S. children aged 1 to 5 years, 1988–2004. Pediatrics 2009;123(3):e376-e385.

Introductory Framework
Organism and the Environment

Non-living collections → "Primitive" life → Early life → Ecological systems

Why the development of ecological complexity?

Abstract Biochemical Model of Evolutionary-Ecological Life on Earth

Non-living *collections* things-molecules

-Static
-Lack of organization
-High *entropy* (low order)

Death

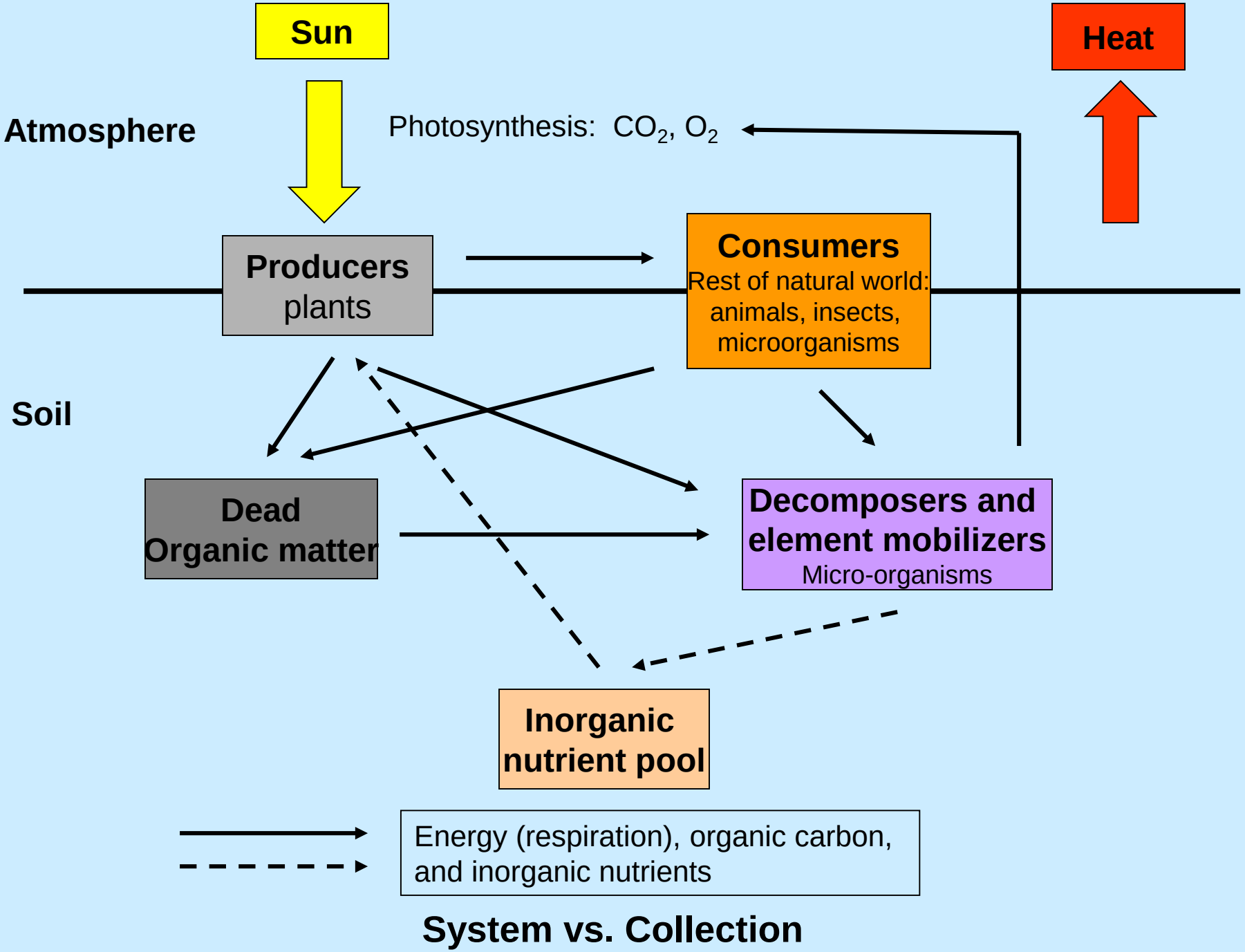
Transition to life

Keys are (1) energy source: the sun and means to utilize solar energy and (2) means to maintain identity

Living *eco-system*

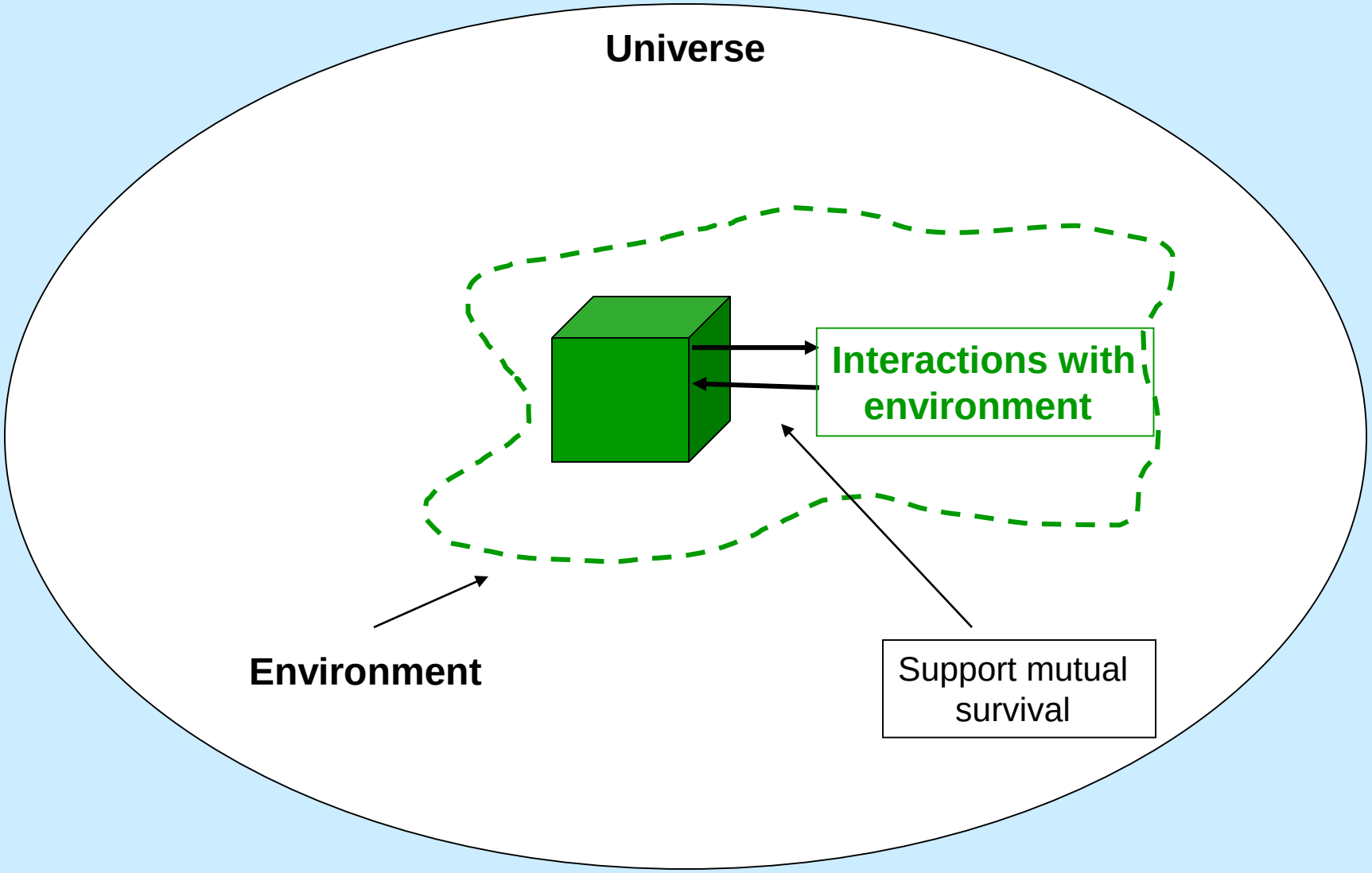
-Dynamic, organized, complex integrated
-Self reproducing (DNA) with maintenance of identity
-Low *entropy* (high order)
-Opportunity for mutation and slow *selection* process

Evolution



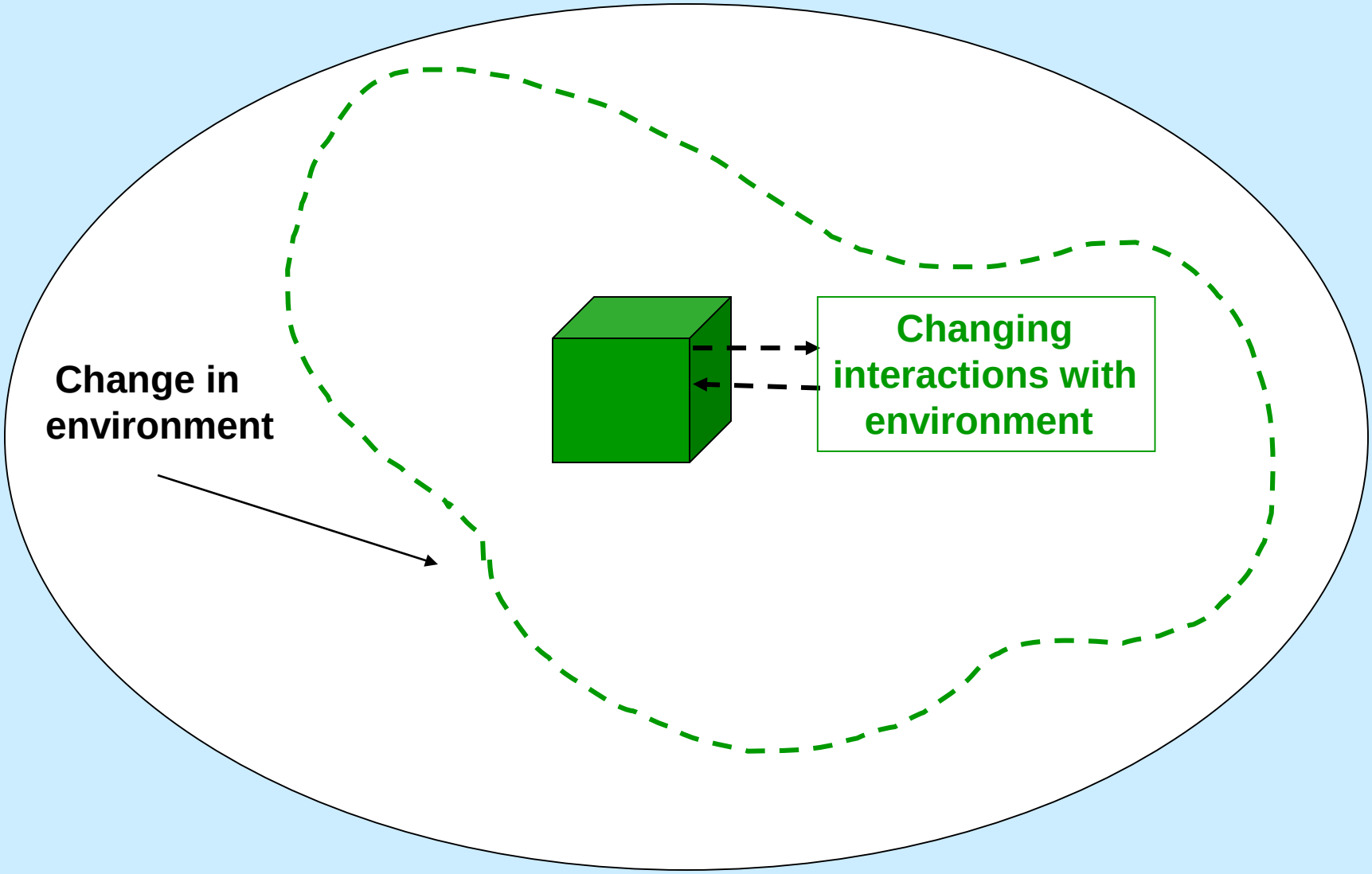
System vs. Collection

Organisms and the Environment



Fitness: organism lives successfully within an environmental context.

Organisms and the Environment: Evolutionary Implications



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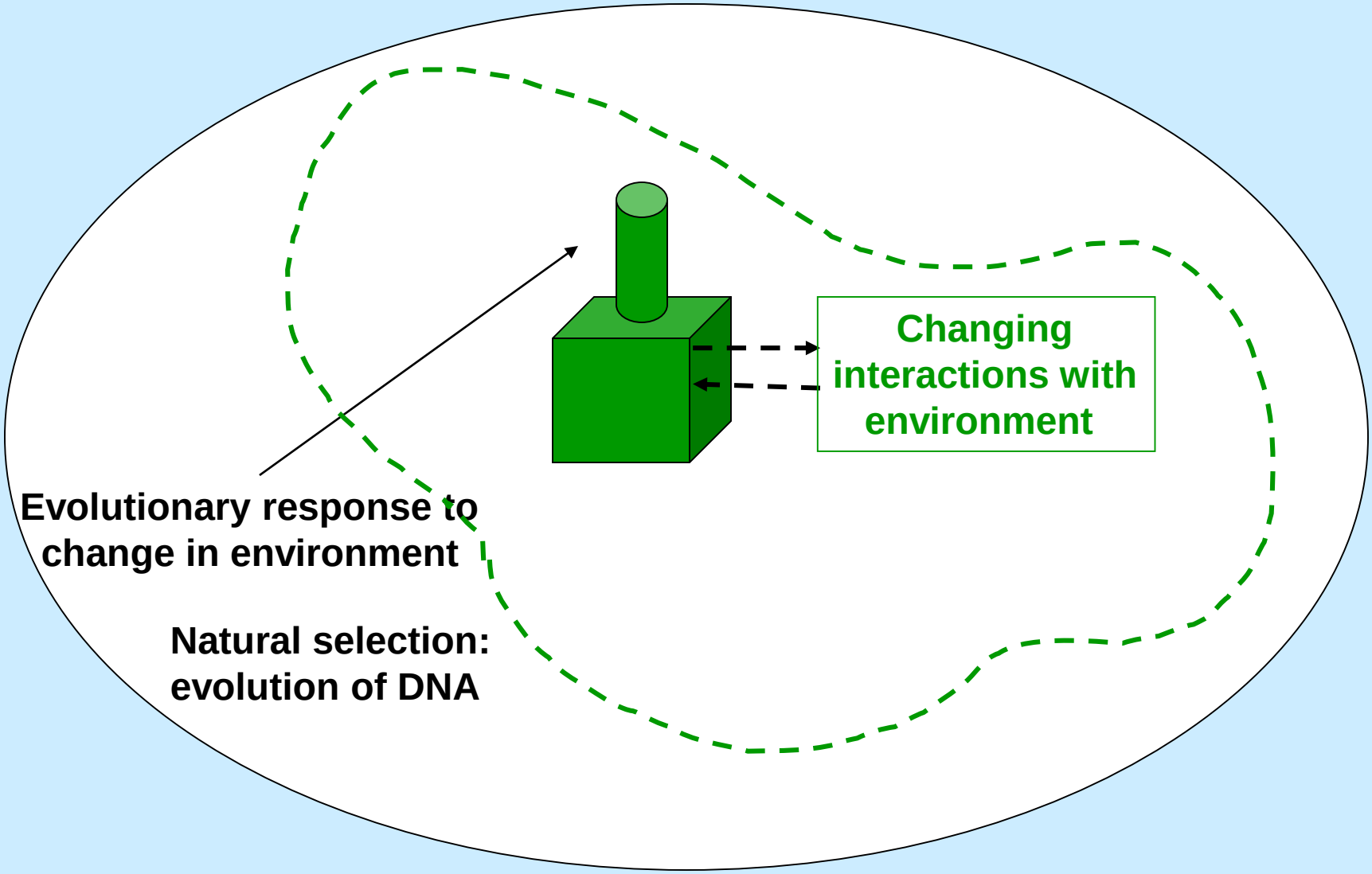
Organisms and the Environment: Evolutionary Implications



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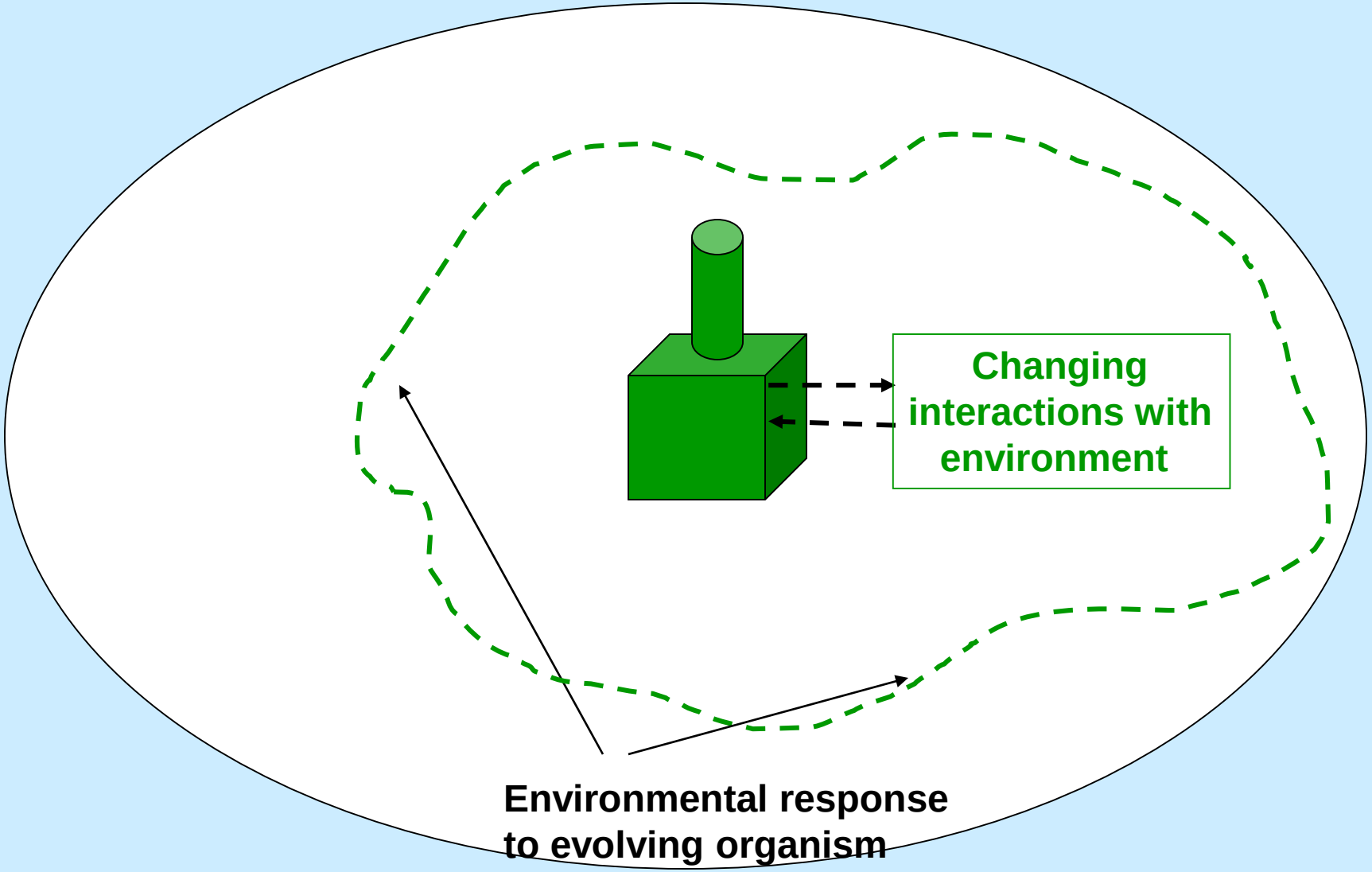

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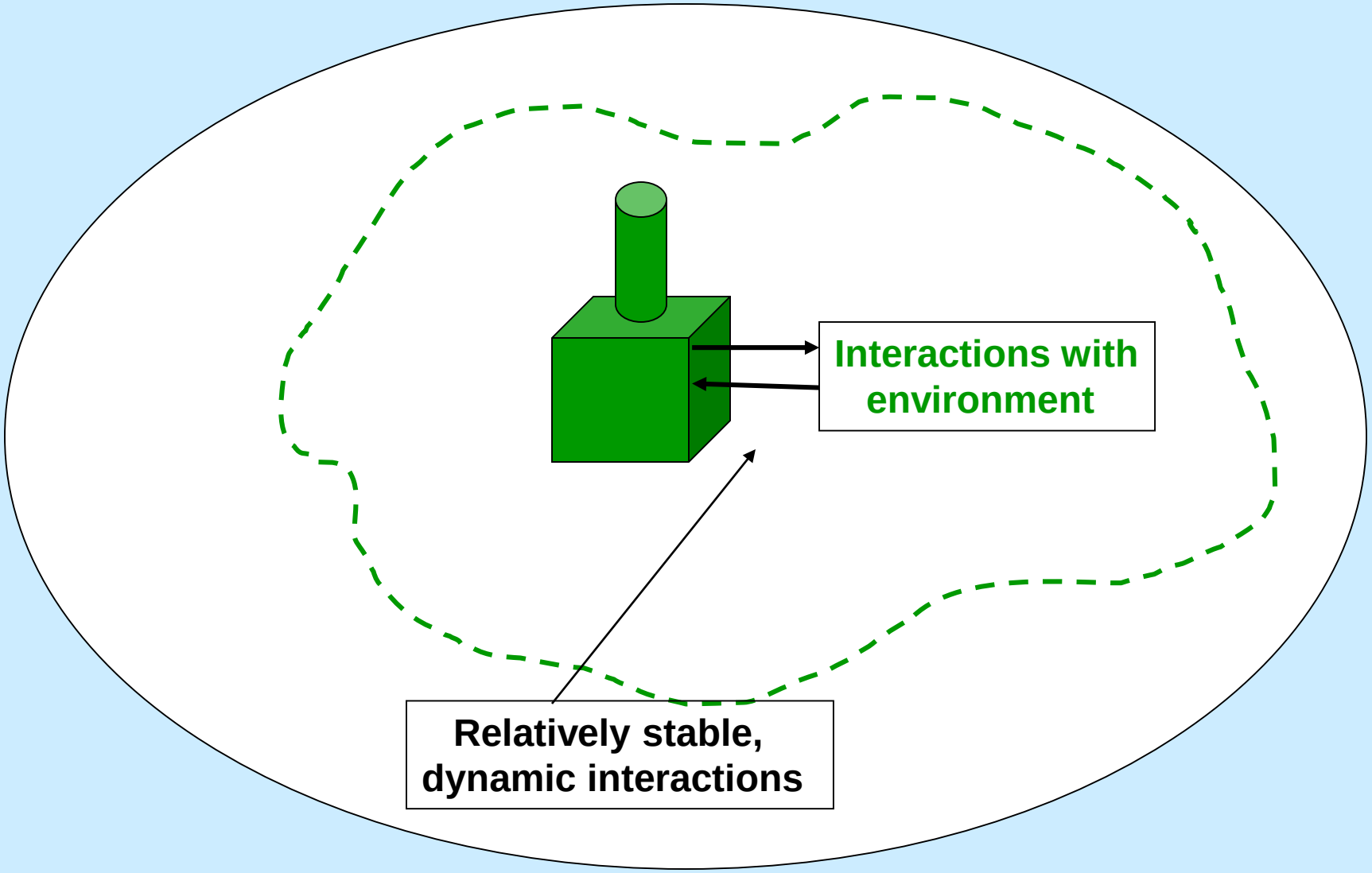
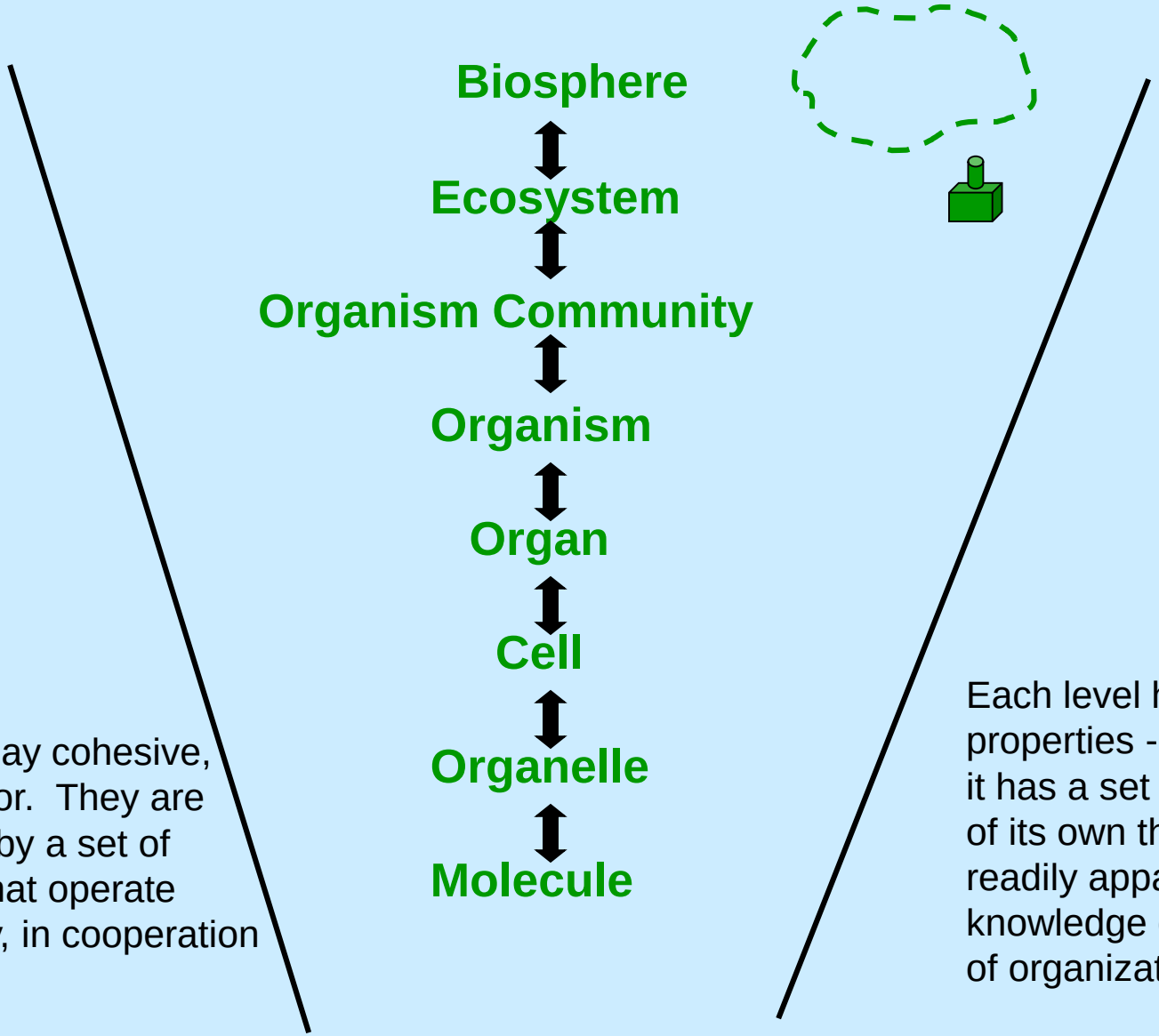
Organisms and the Environment: Evolutionary Implications



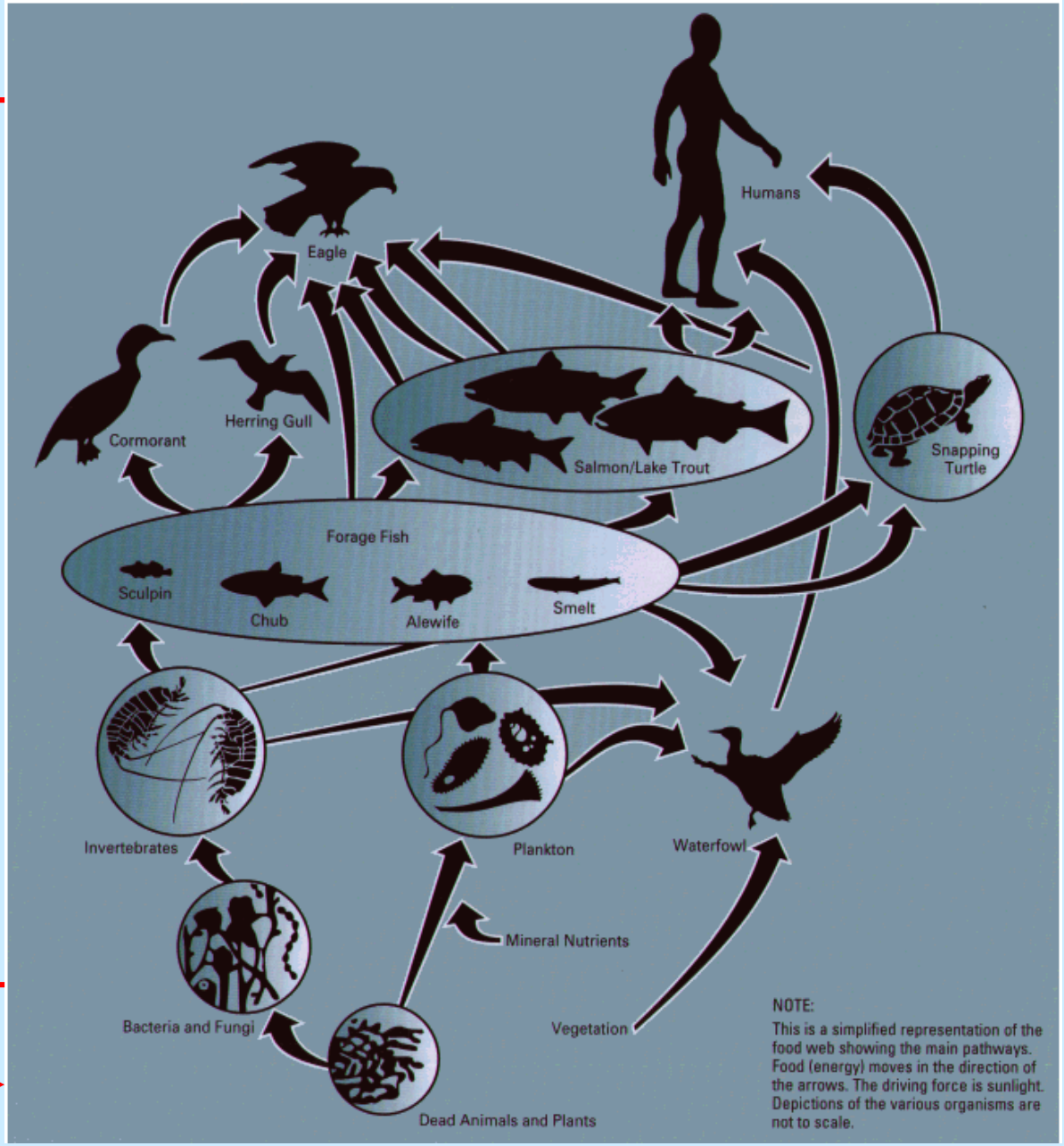
Fitness: organism lives successfully within an environmental context.

Hierarchical Organization of Life (Systems)



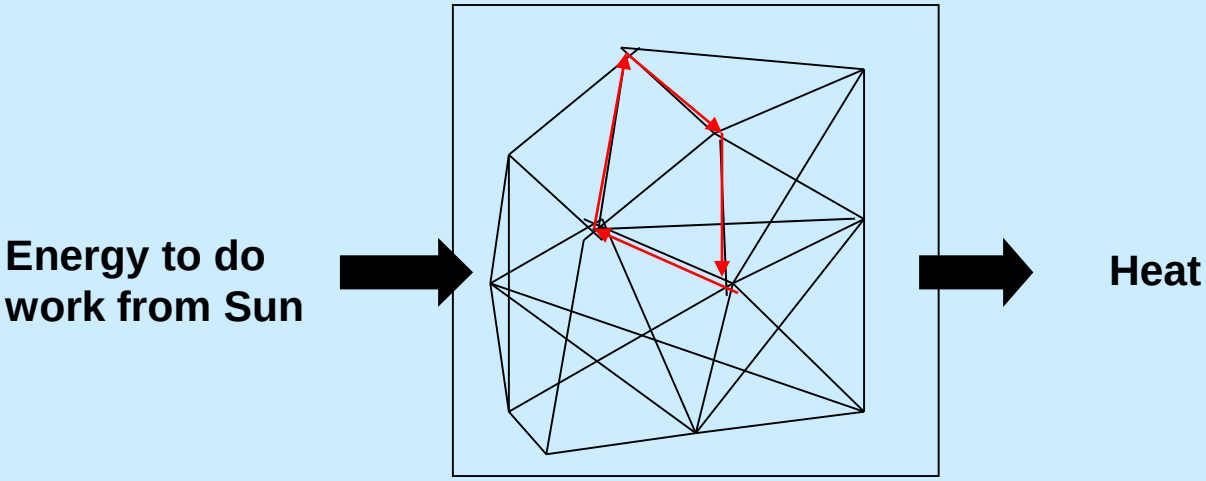
Systems display cohesive, unitary behavior. They are characterized by a set of components that operate together/jointly, in cooperation

Each level has ***system*** properties - meaning it has a set of properties of its own that are not readily apparent from knowledge of lower levels of organization.



http://www.epa.gov/glnpo/atlas/index.html

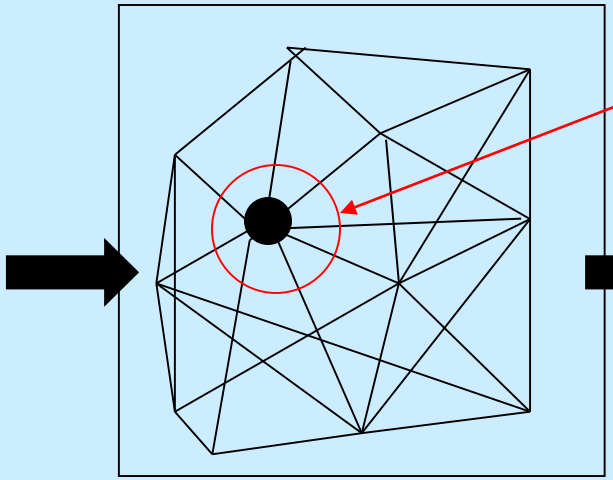
Abstract Model of Native Biosphere



Highly ordered <u>system</u>
Based on <u>connections</u> and cycles

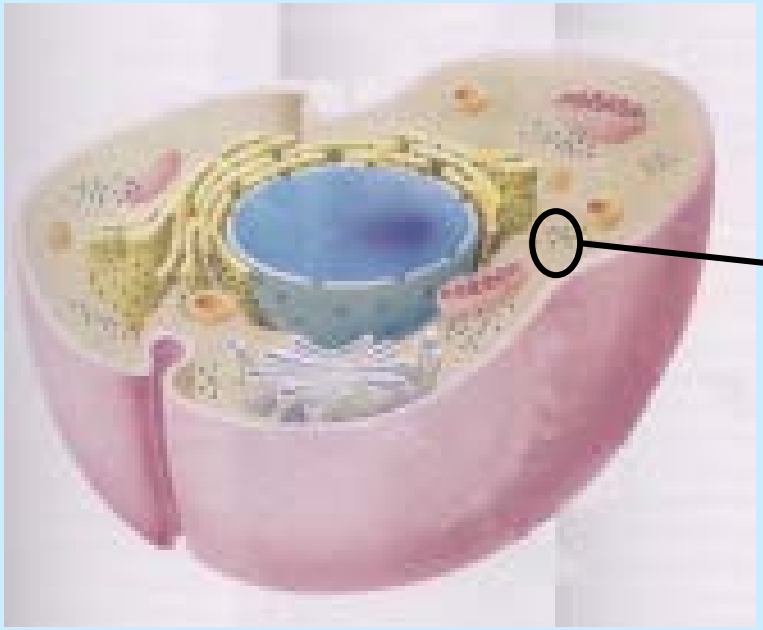
Model emphasizes that everything is connected to everything else.
Concept of Fitness

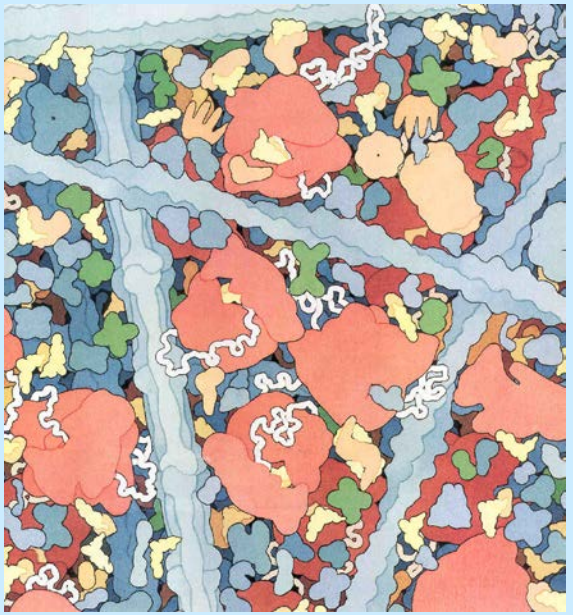
Abstract Model of Cell



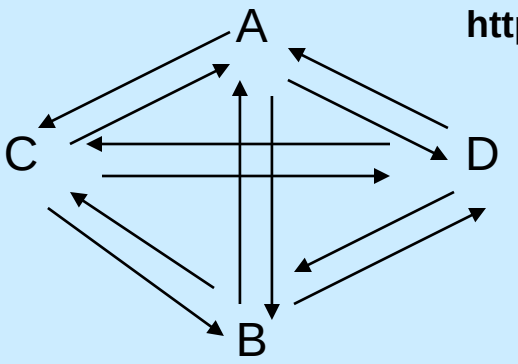
Highly ordered system
Based on connections and cycles

The Cell: Lowest Hierachical Level





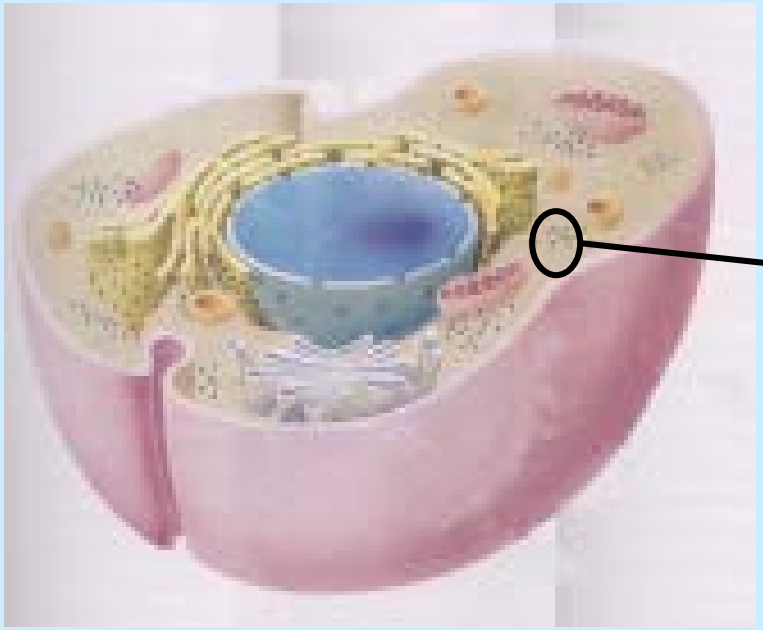
David Goodsell
http://mgl.scripps.edu.people/goodsell

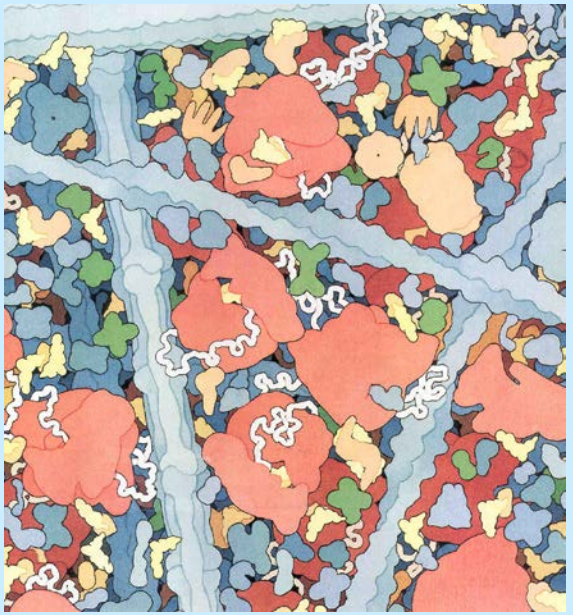


Everything is connected to everything else
and is functional within an environmental/ecological context

Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN



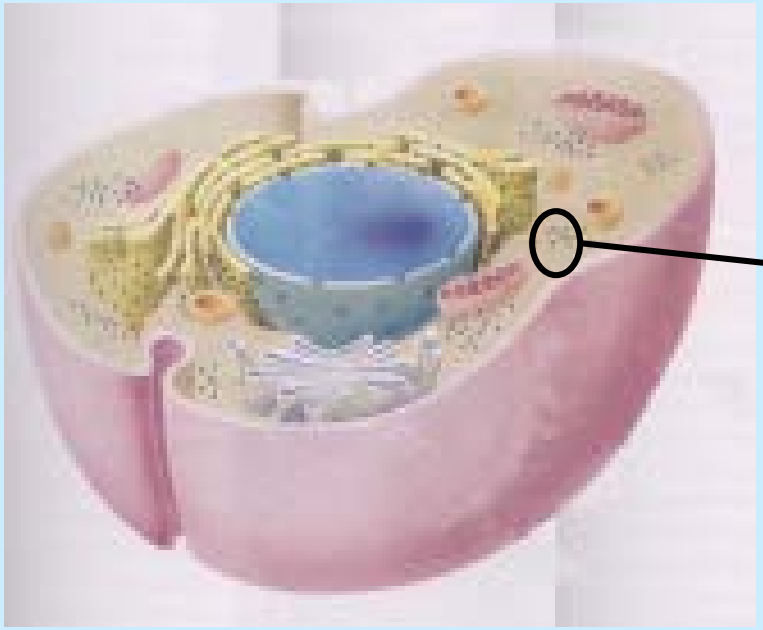


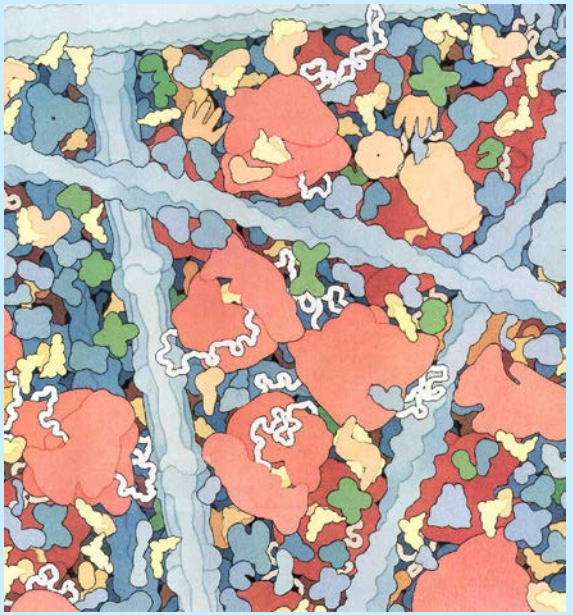
Replication

DNA ← DNA

Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN





Replication

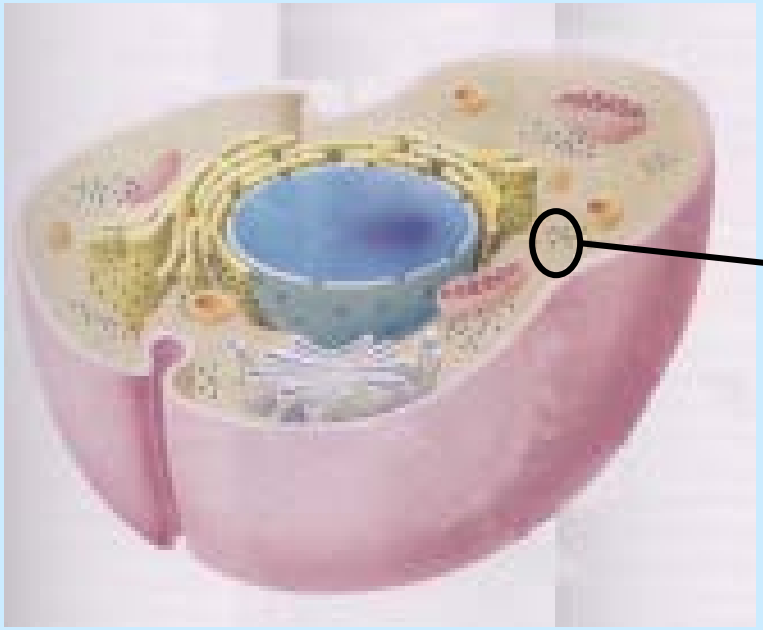
DNA ← DNA

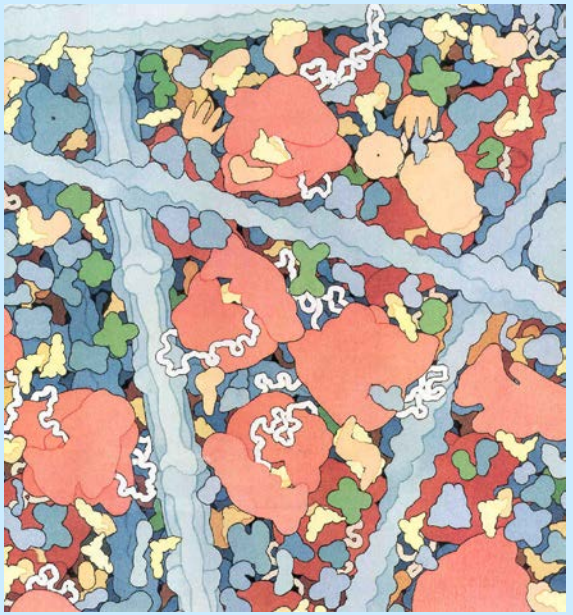
Errors ↓ ↑ Repair

DNA'(mutation)

Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN





Replication

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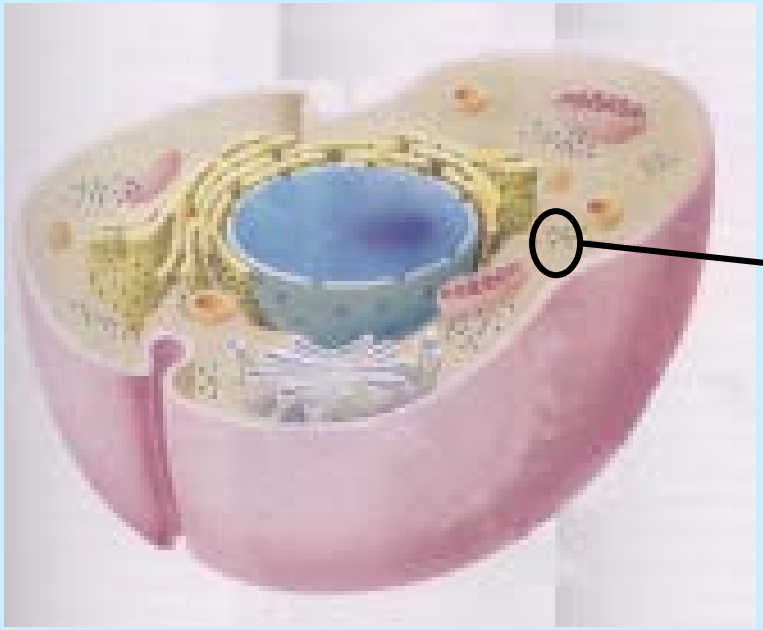
DNA'(mutation)

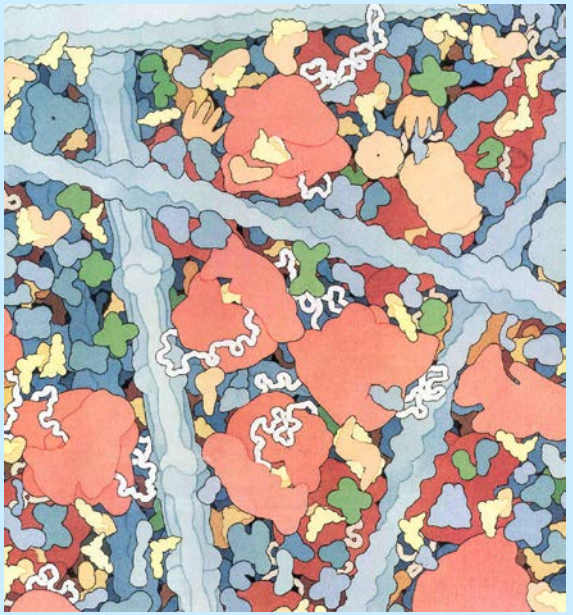
↓ Selection

Evolution

Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN





Replication

DNA ← DNA → RNA → Protein (enzymes)

Errors ↓ ↑ Repair

DNA'(mutation)

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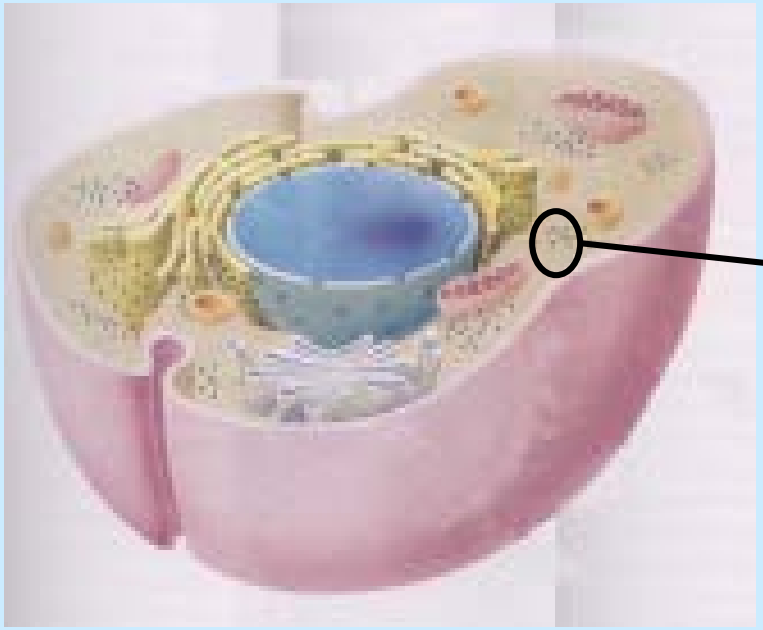
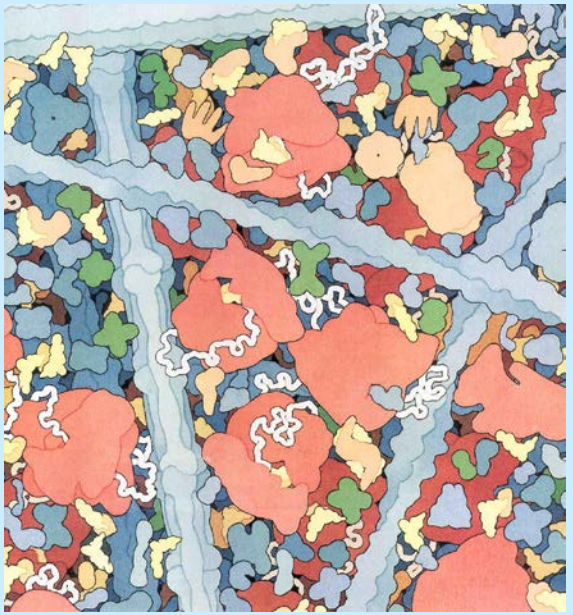
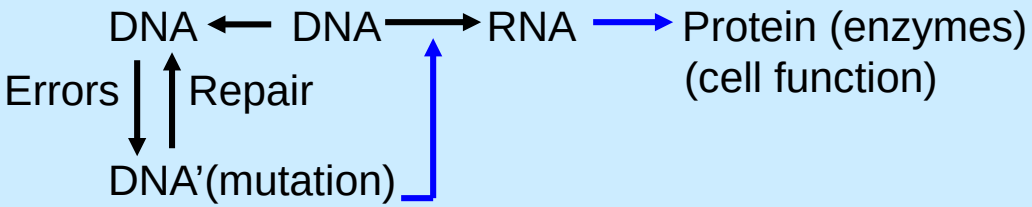




Replication



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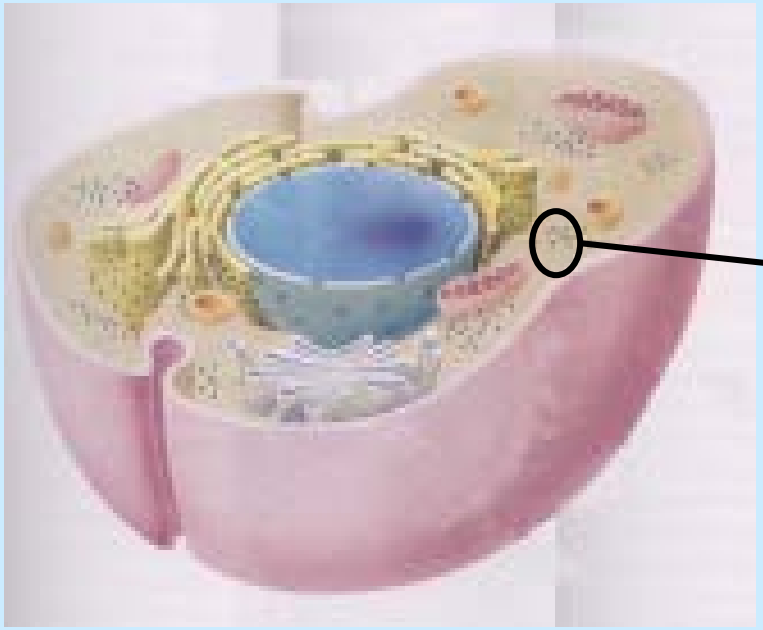
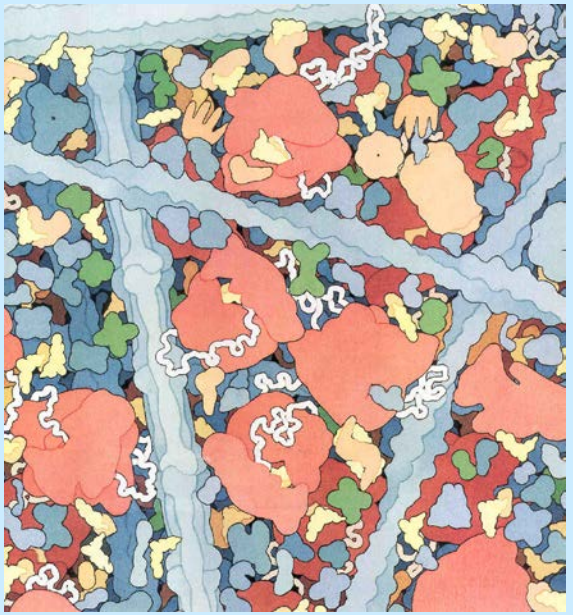
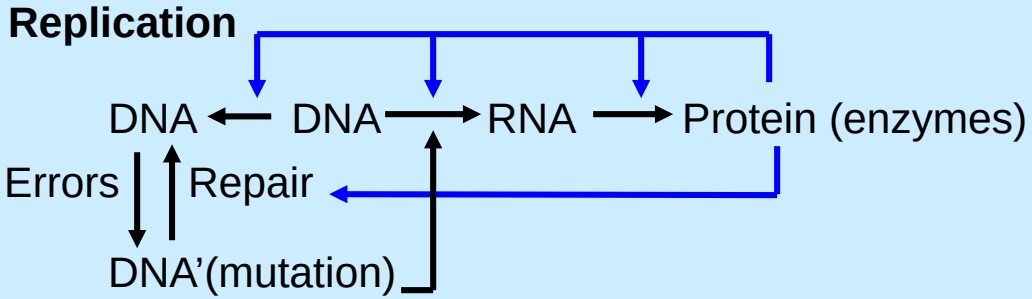
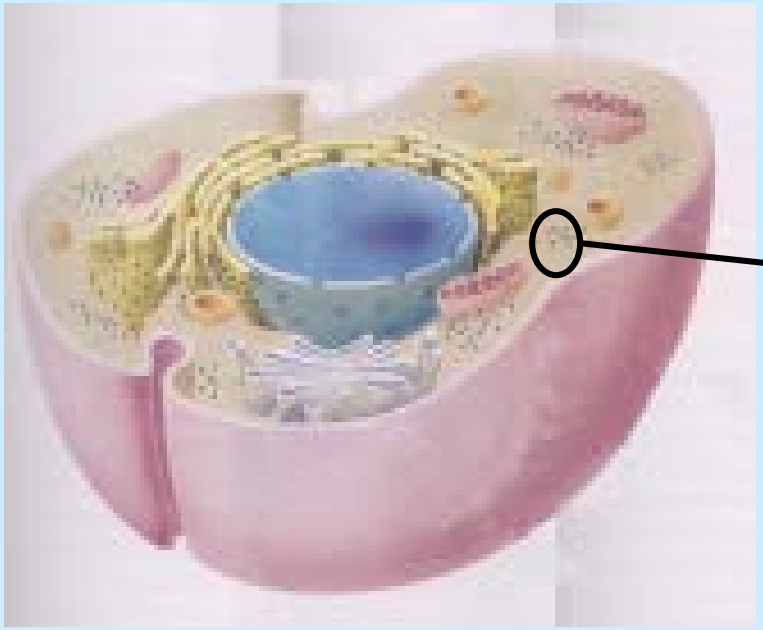


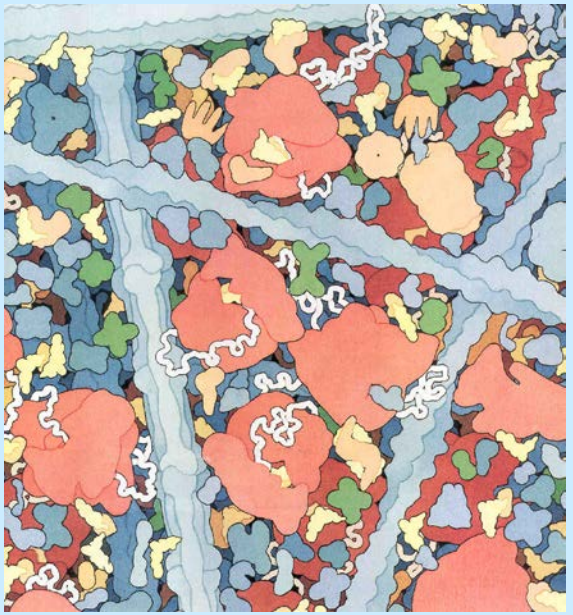




Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN





Replication

DNA ← DNA → RNA → Protein (enzymes)

Errors ↓ ↑ Repair

DNA'(mutation)

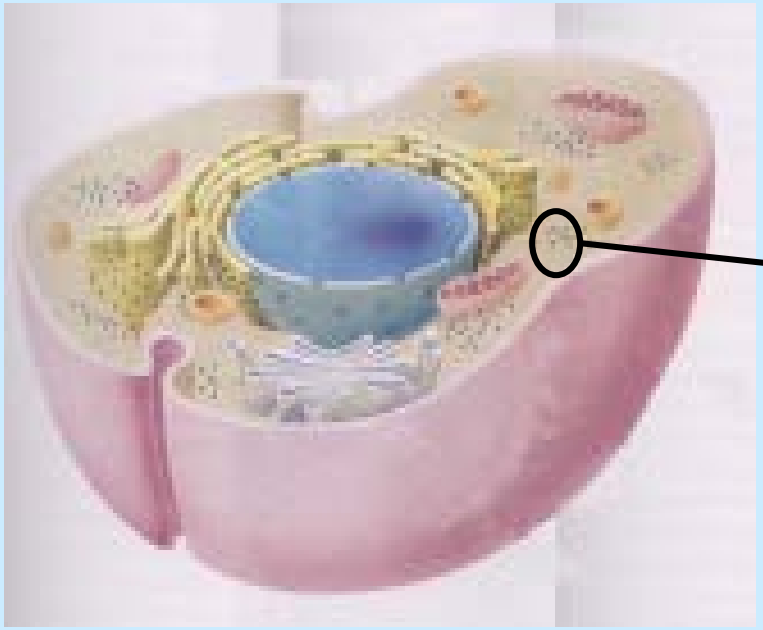
Starting materials for making DNA, RNA, protein

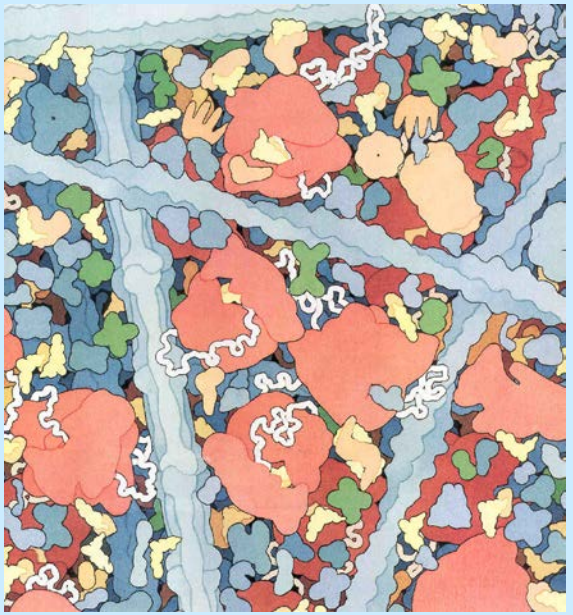
Starting materials for making starting materials

Energy source (ATP) to make starting materials

Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN





Replication

DNA ← DNA → RNA → Protein (enzymes)

Errors ↓ ↑ Repair

DNA'(mutation)

Solar Energy

Starting materials for making DNA, RNA, protein

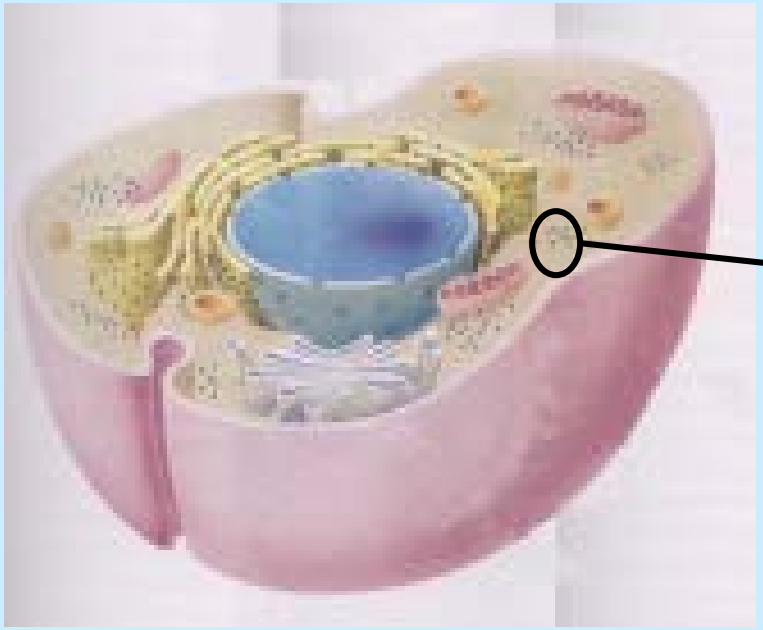
Starting materials for making starting materials

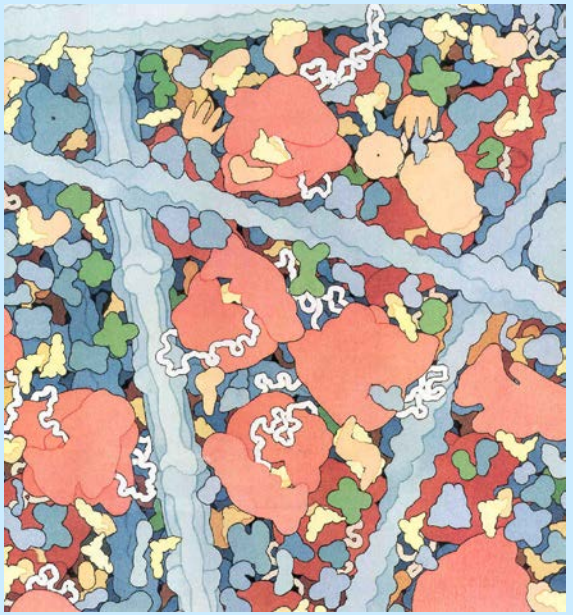
Energy source (ATP) to make starting materials

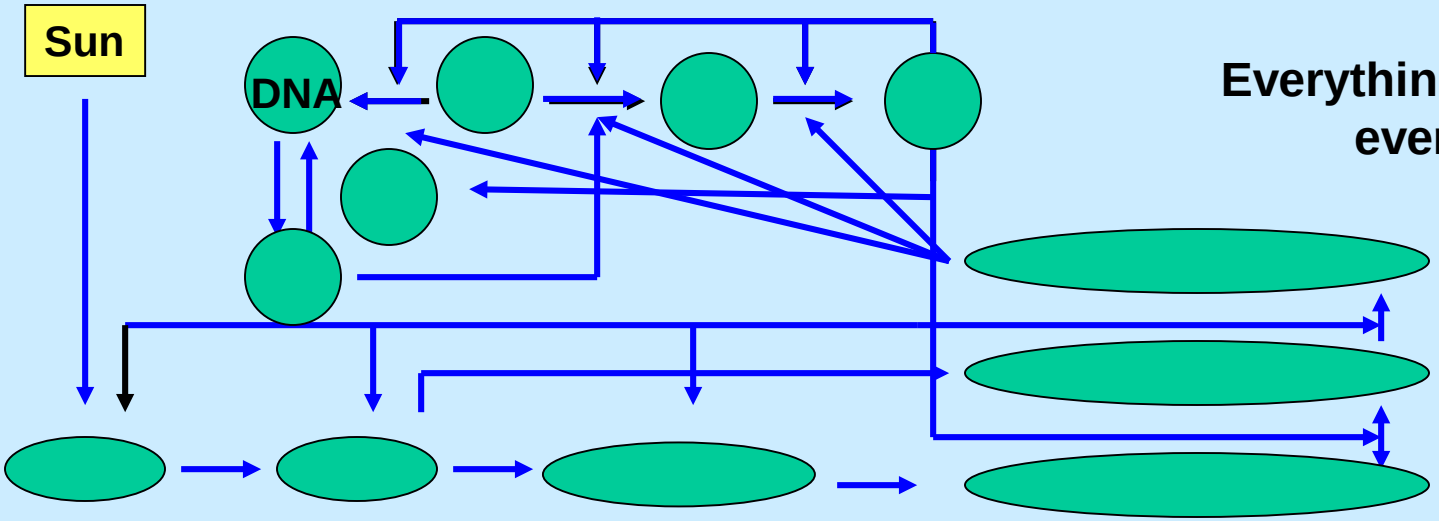
Photo-synthesis → Glucose metabolism → Oxidative phosphorylation

Role of DNA in Cellular Identity?

DNA → RNA → PROTEIN







Everything is connected to everything else

Comments on Everything is Connected to Everything Else

Is cellular identity basically the *information* stored in a molecule? DNA?

DNA → mRNA → protein → cell function

Or is it rooted in "everything is connected to everything else?"

DNA structure: genetic identity

Most general, straightforward way to alter identity is through modifying/mutating DNA structure-base sequence

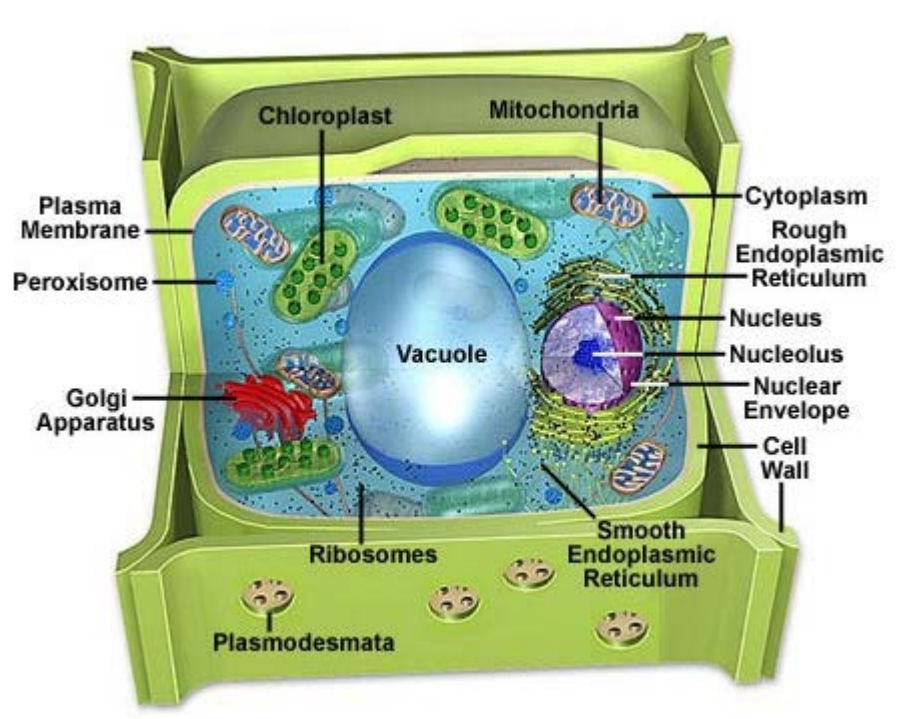
Expansion to include *epi-genetic* mechanisms that do not alter DNA sequence but modify DNA expression patterns (mRNA and protein)

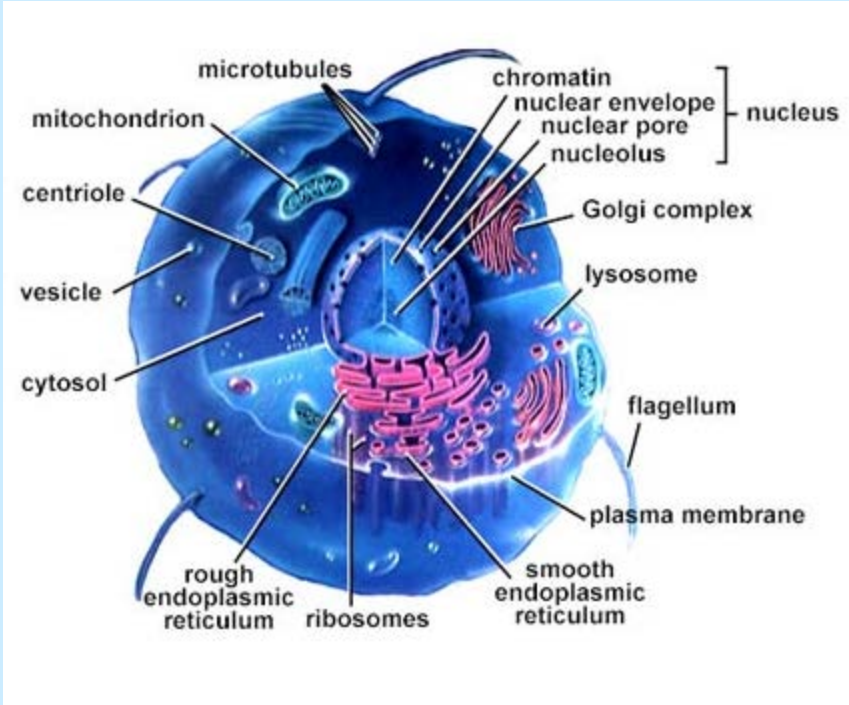
Creating a cell: the Venter *synthetic* cell (Science, 2010, 329:52-6)

-Simple enucleated cell plus insertion of full DNA sequence into closely related enucleated cell*

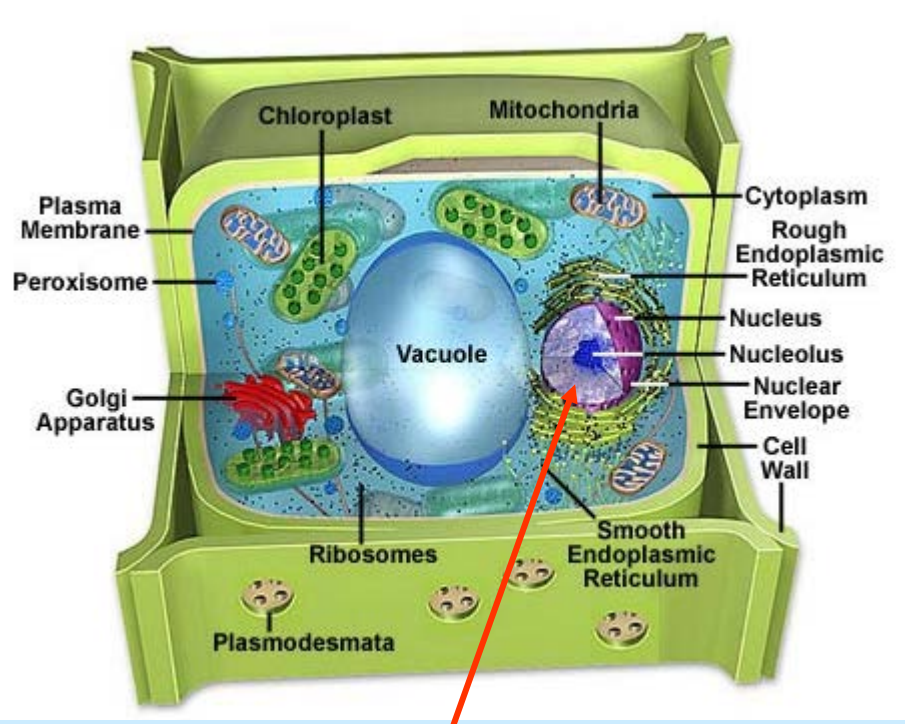
* Methods that combine (a) DNA polymerase dependent synthesis of DNA sequences with (b) stable means to link them together and express the resultant DNA sequence in yeast.

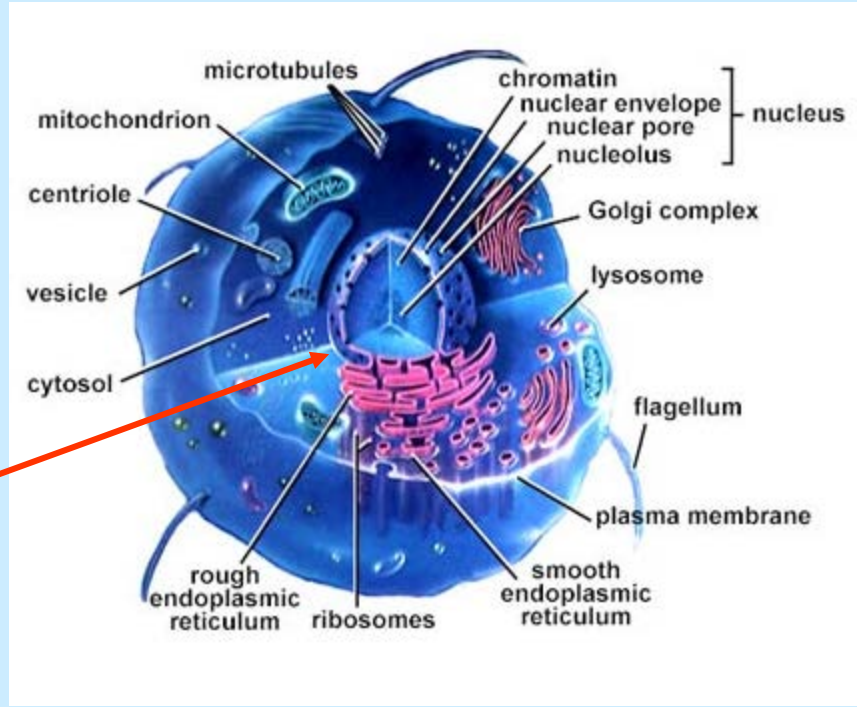
Cell Identity and its Maintenance: the Venter Experiment





Cell Identity and its Maintenance: the Ventor Experiment





DNA: molecular repository of *information*

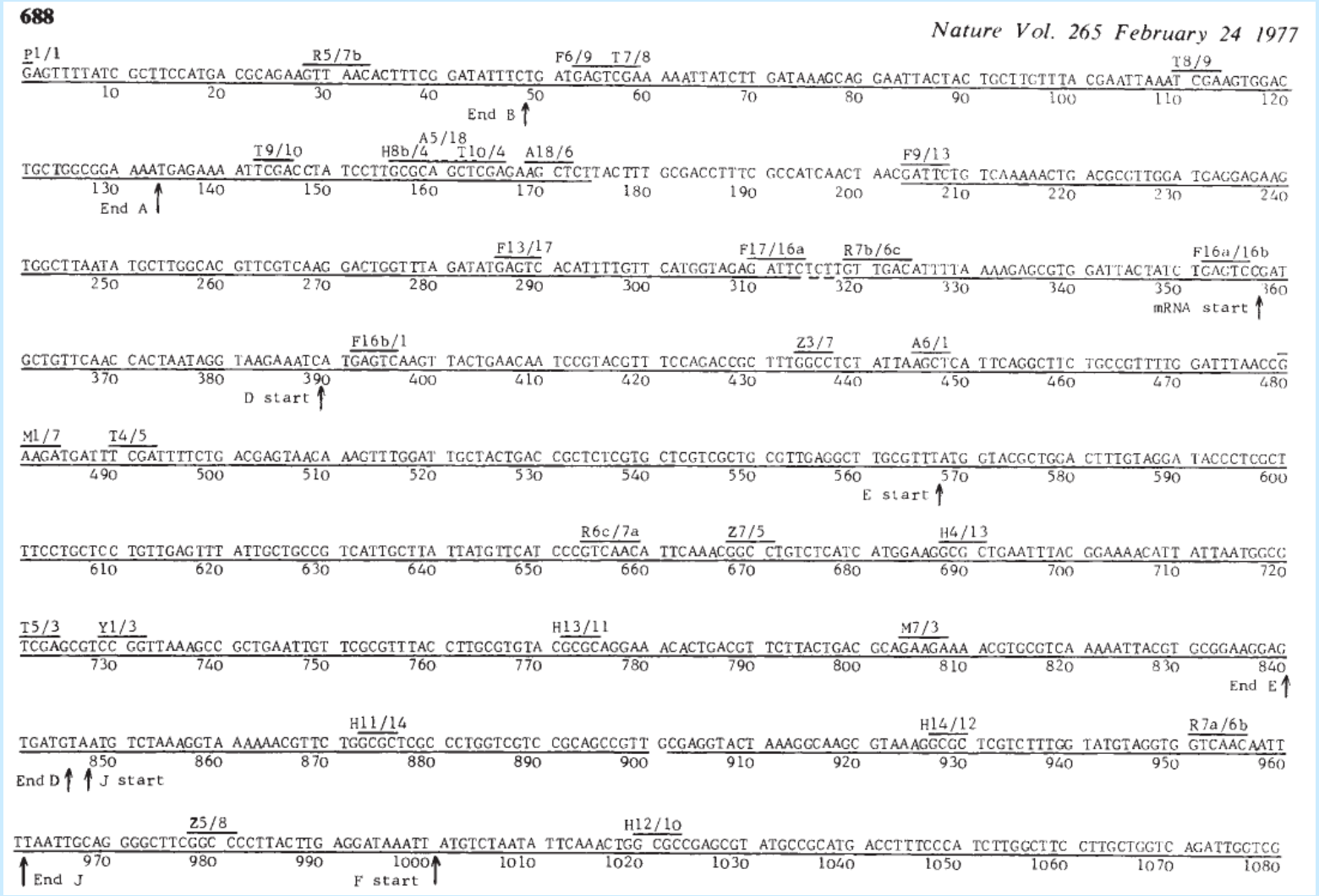
Rest of Cell: role in cell identity?

Partial Base Sequence of Phi-X 174 Bactiophage

```
ORIGIN              1 gagttttatc gcttccatga cgcag
atgagtcgaa         61 aaattatctt gataaagcag gaattac
cgaagtggac        121 tgctggcgga aaatgagaaa attcgac
ctcttacttt        181 gcgacctttc gccatcaact aacgatt
tgaggagaag        241 tggcttaata tgcttggcac gttcgtc
acattttgtt        301 catggtagag attctcttgt tgacatt
tgagtccgat        361 gctgttcaac cactaatagg taagaaa
tccgtacgtt        421 tccagaccgc tttggcctct attaagc
gatttaaccg        481 aagatgattt cgattttctg acgagta
cgctctcgtg        541 ctcgtcgctg cgttgaggct tgcgttt
taccctcgct        601 ttcctgctcc tgttgagttt attgctg
cccgtcaaca        661 ttcaaacggc ctgtctcatc atggaag
attaatggcg        721 tcgagcgtcc ggttaaagcc gctgaat
cgcgcaggaa        781 acactgacgt tcttactgac gcagaag
gcggaaggag        841 tgatgtaatg tctaaaggta aaaaacg
cgcagccgtt        901 gcgaggtact aaaggcaagc gtaaagg
gtcaacaatt        961 ttaattgcag gggcttcggc cccttac
ttcaaactgg       1021 cgccgagcgt atgccgcatg acctttc
agattggtcg       1081 tcttattacc atttcaacta ctccggt
tggacgccgt       1141 tggcgctctc cgtctttctc cattgcg
ctgtagacat       1201 ttttactttt tatgtccctc atcgtca
agttcatgaa       1261 ggatggtgtt aatgccactc ctctccc
ttgaccatgc       1321 cgcttttctt ggcacgatta accctga
tgtttcaggg       1381 ttatttgaat atctataaca actattt
gtaccgaggc       1441 taaccctaat gagcttaatc aagatga
gccatctcaa       1501 aaacatttgg actgctccgc ttcctcc
tgacgacttc       1561 taccacatct attgacatta tgggtct
atactgacca       1621 agaacgtgat tacttcatgc agcgtta
gaggtaaaac       1681 ctcttatgac gctgacaacc gtccttt
gggcatctgg       1741 ctatgatgtt gatggaactg accaaac
gtgttcaaca       1801 gacctataaa cattctgtgc cgcgttt
tgtttactct       1861 tgcgcttgtt cgttttccgc ctactgc
acgctaaagg       1921 tgctttgact tataccgata ttgctgg
tgccgccgcg       1981 tgaaatttct atgaaggatg ttttccg
ttaagattgc       2041 tgagggtcag tggtatcgtt atgcgcc
accttcttga       2101 aggcttccca ttcattcagg aaccgcc
```

F. Sanger (1977) 5386 nucleotides total: 11 genes, circular, single stranded

DNA and *Information*



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Nature Vol. 265 February 24 1977

P1/1
GAGTTTTATC GCTTCCATGA CGCAGAAGTT R5/7b AACACTTTCG GATATTTCTG F6/9 T7/8 ATGAGTCGAA AAATTATCTT GATAAAGCAG GAATTACTAC TGCTTCTTTA CGAATTAAAT T8/9 CGAAGTGGAC
10 20 30 40 50 60 70 80 90 100 110 120
End B

T9/10 H8b/4 A5/18 T10/4 A18/6 F9/13
TGCTGGCGGA AAATGAGAAA ATTCGACCTA TCCTTGCGCA GCTCGAGAAG CTCTTACTTT GCGACCTTTC GCCATCAACT AACGATTCTG TCAAAAACTG ACGCGTTGGA TGAGGAGAAG
130 140 150 160 170 180 190 200 210 220 230 240
End A

F13/17 F17/16a R7b/6c F16a/16b
TGGCTTAATA TGCTTGGCAC GTTCGTCAAG GACTGGTTTA GATATGAGTC ACATTTTGTT CATGGTAGAG ATTCTCTTGT TGACATTTTA AAAGAGCGTG GATTACTATC TGAGTCCGAT
250 260 270 280 290 300 310 320 330 340 350 360
mRNA start

F16b/1 Z3/7 A6/1
GCTGTTCAAC CACTAATAGG TAAGAAATCA TGAGTCAAGT TACTGAACAA TCCGTACGTT TCCAGACCGC TTTGGCCTCT ATTAAGCTCA TTCAGGCTTC TGCCGTTTTG GATTTAACCG
370 380 390 400 410 420 430 440 450 460 470 480
D start

M1/7 T4/5
AAGATGATTT CGATTTTCTG ACGAGTAACA AAGTTTGGAT TGCTACTGAC CGCTCTCGTG CTCGTCGCTG CGTTGAGGCT TGCGTTTATG GTACGCTGGA CTTTGTAGGA TACCCTCGCT
490 500 510 520 530 540 550 560 570 580 590 600
E start

R6c/7a Z7/5 H4/13
TTCCTGCTCC TGTTGAGTTT ATTGCTGCCG TCATTGCTTA TTATGTTCAT CCCGTCAACA TTCAAACGGC CTGTCTCATC ATGGAAGGCG CTGAATTTAC GGAAAACATT ATTAATGGCC
610 620 630 640 650 660 670 680 690 700 710 720

T5/3 Y1/3 H13/11 M7/3
TCGAGCGTCC GGTTAAAGCC GCTGAATTGT TCGCGTTTAC CTTGCGTGTA CGCGCAGGAA ACACTGACGT TCTTACTGAC GCAGAAGAAA ACGTGCGTCA AAAATTACGT GCGGAAGGAG
730 740 750 760 770 780 790 800 810 820 830 840
End E

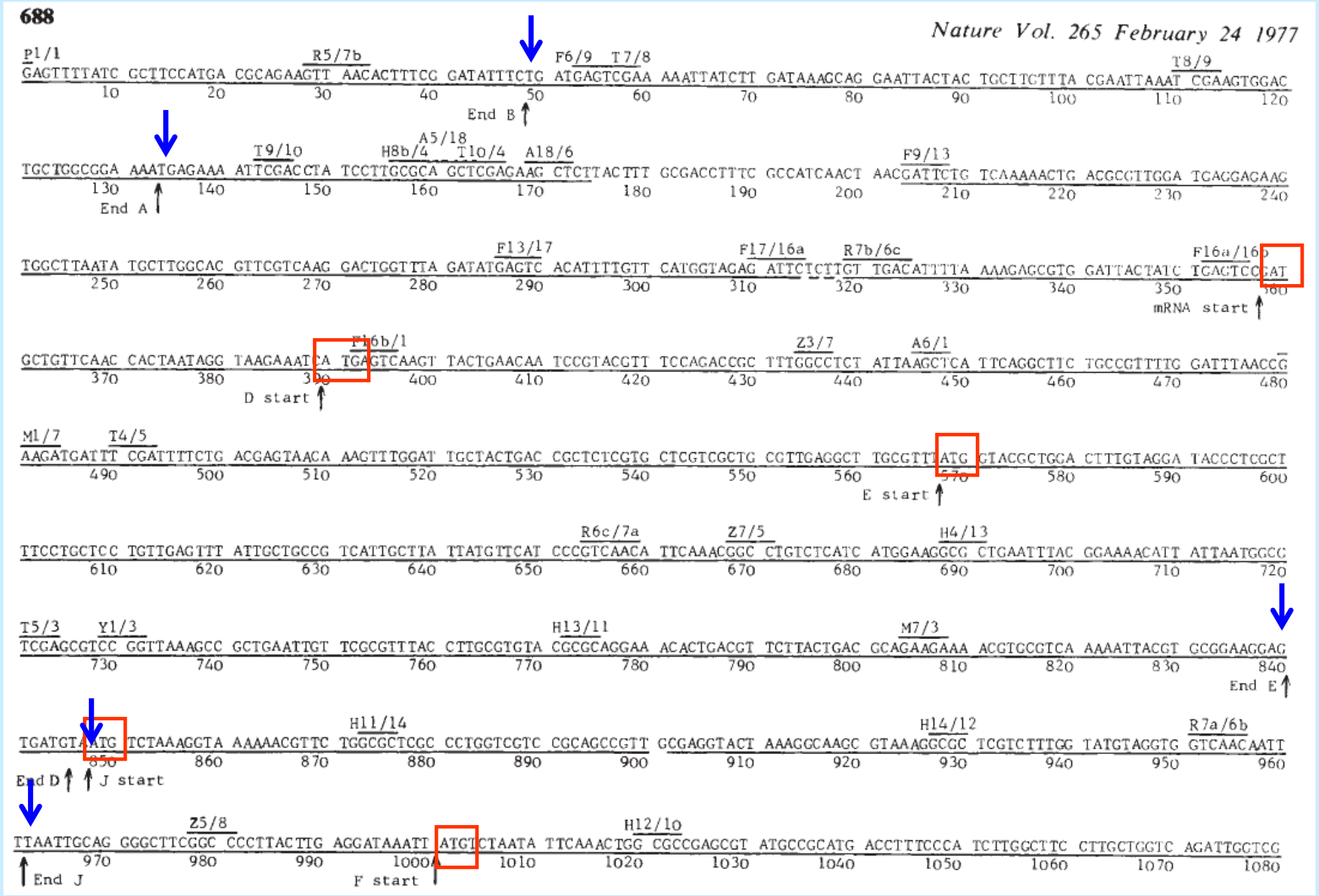
H11/14 H14/12 R7a/6b
TGATGTAATG TCTAAAGGTA AAAAACGTTC TGGCGCTCGC CCTGGTCGTC CGCAGCCGTT GCGAGGTACT AAAGGCAAGC GTAAAGGCGC TCGTCTTTGG TATGTAGGTG GTCAACAATT
850 860 870 880 890 900 910 920 930 940 950 960
End D J start

Z5/8 H12/10
TTAATTGCAG GGGCTTCGGC CCCTTACTTG AGGATAAATT ATGTCTAATA TTCAAACTGG CGCCGAGCGT ATGCCGCATG ACCTTTCCCA TCTTGGCTTC CTTGCTGGTC AGATTGGTCG
970 980 990 1000 1010 1020 1030 1040 1050 1060 1070 1080
End J F start

***Information* is only *Information* if it is understood!**

Requirement of donor and acceptor: information exchange

DNA and *Information*



How is it that mRNA synthesis starts only at these sites?

What if mRNA synthesis started randomly at other sites?

Comments on Everything is Connected to Everything Else

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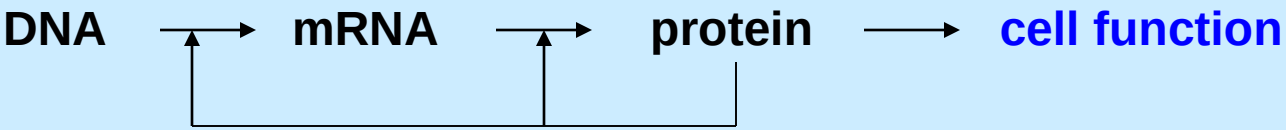
DNA → mRNA → protein → cell function

Or is it rooted in "everything is connected to everything else?"



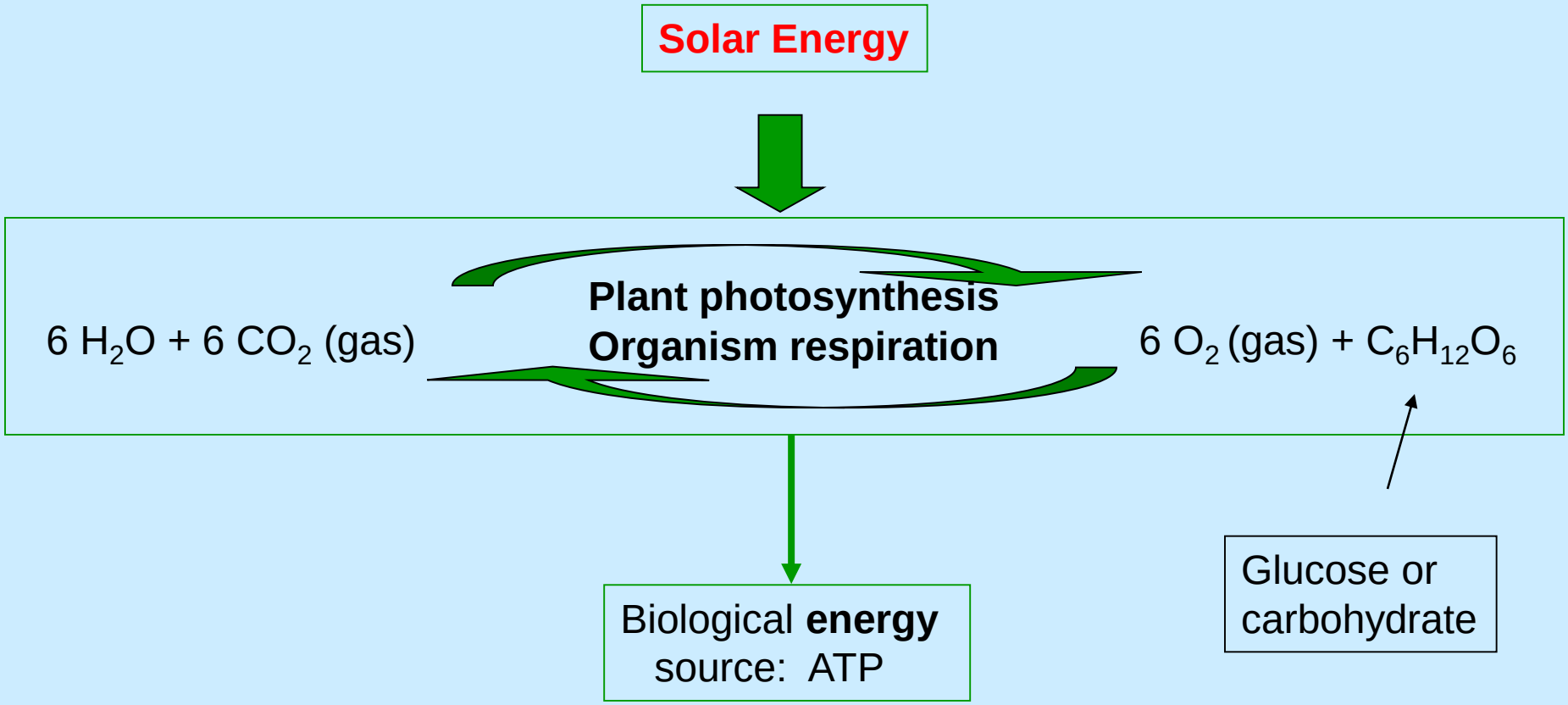
(mRNA polymerase) **(ribosome)**

Contributions to sequence selectivity/specificity

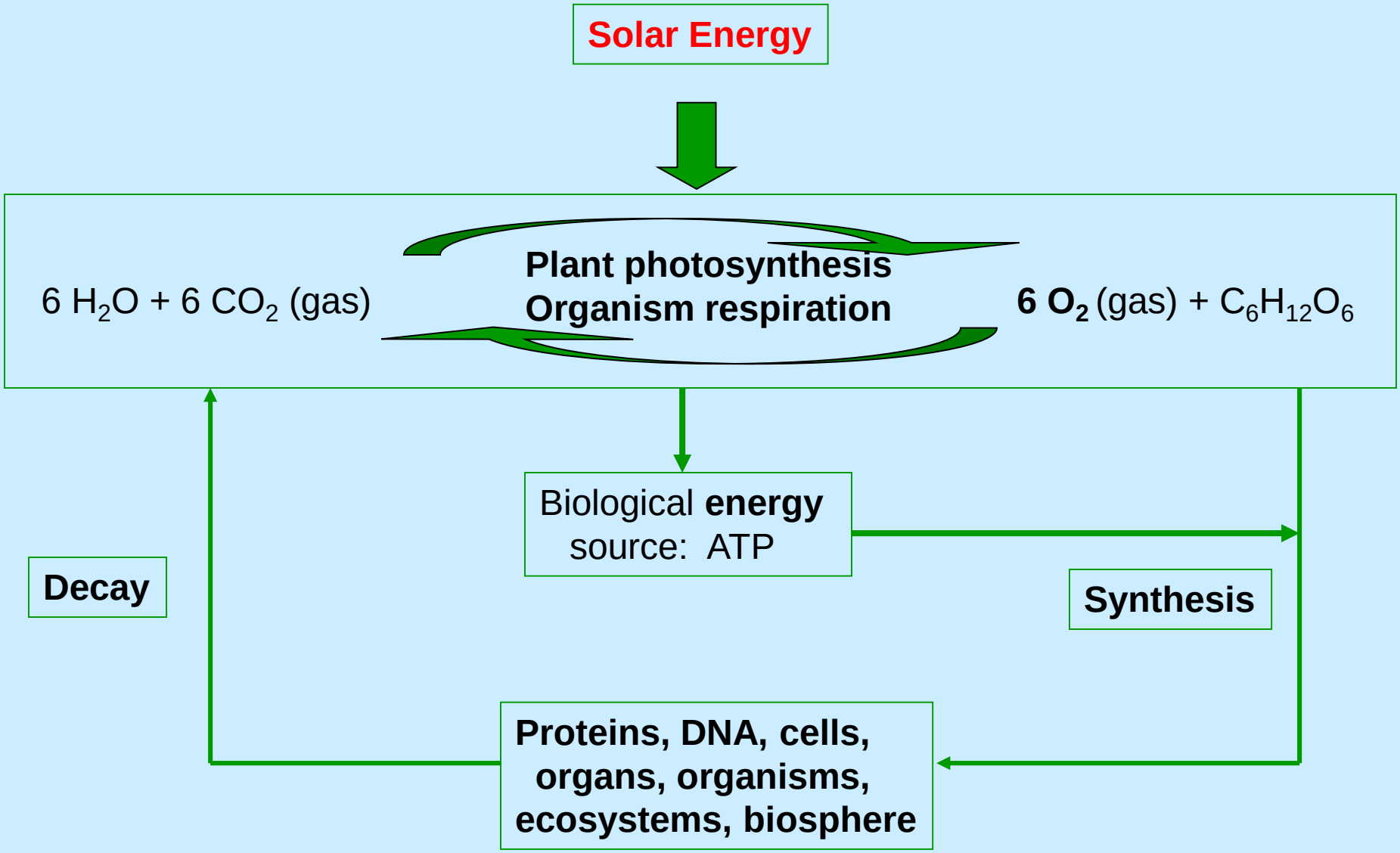
The collaboration of enucleated cell and DNA results in viable cell.

Functional identity results from everything being connected to everything else.

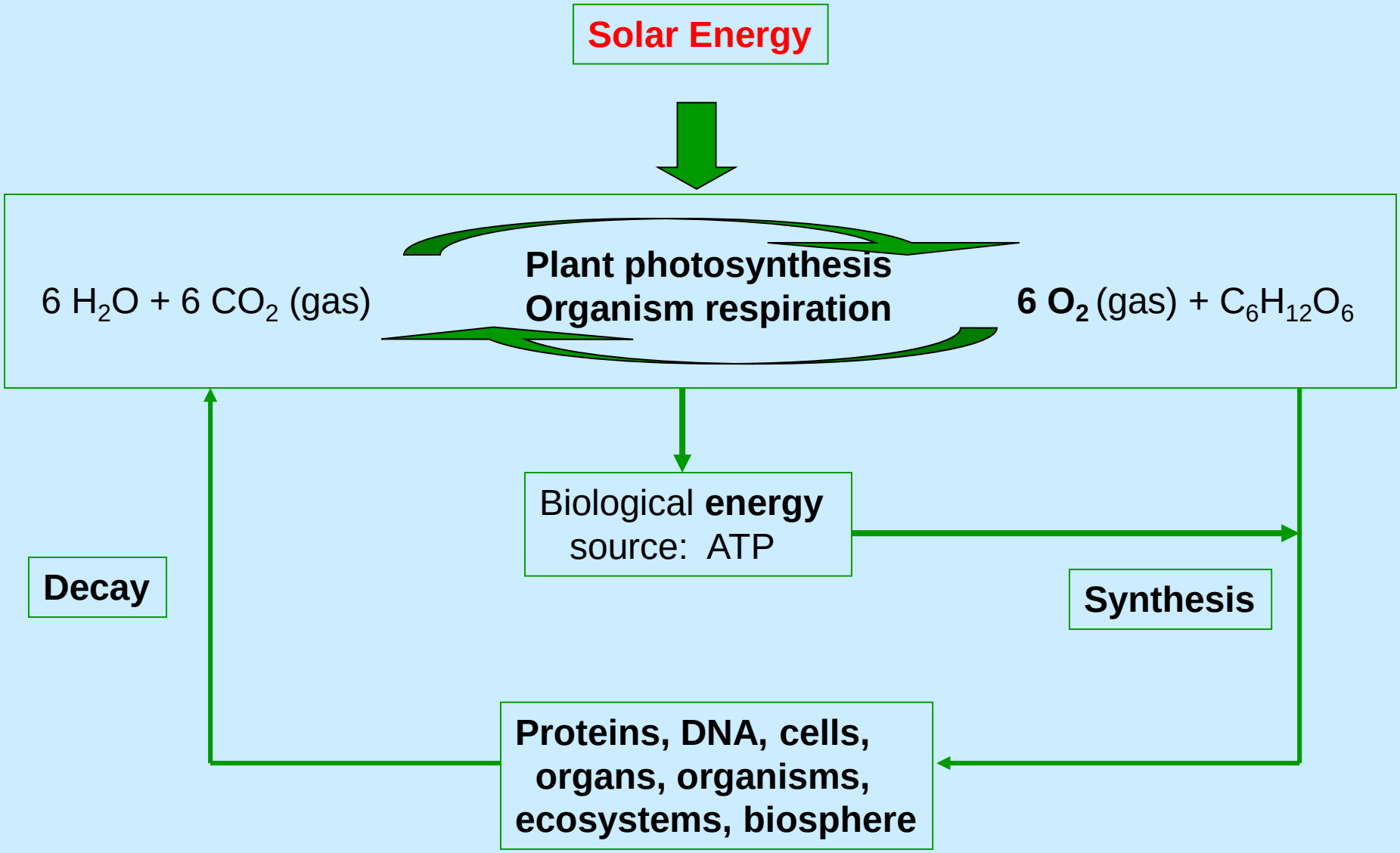
Environmental Adaptation
Interconnectedness of Life



Photosynthesis and respiration make most of the living world go around by providing the means to acquire and use energy.



Photosynthesis and respiration make most of the living world go around by providing the sole source of energy to do work (synthesis).



Solar energy is our life line but …

Organismic Adaptations within the Environment

The sun

Organismic Adaptations within the Environment

The sun

Solar UV radiation causes cancer

Organismic Adaptations within the Environment

The sun

Solar UV radiation causes cancer

<u>Protective mechanisms</u>

Biosphere: ozone layer

Skin: epidermis cell sloughing

Cells: DNA repair

Organismic Adaptations within the Environment

The sun

Solar UV radiation causes cancer

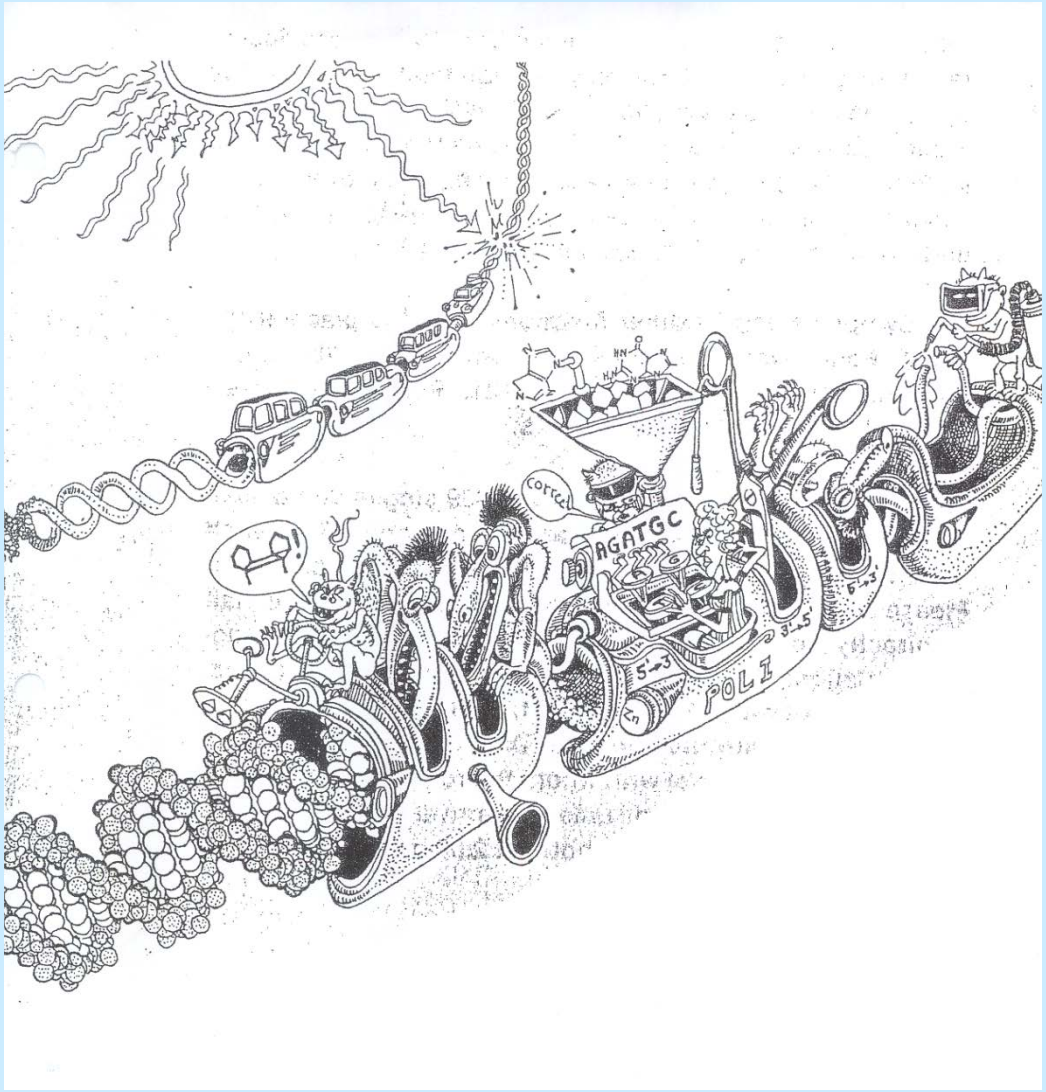
<u>Protective mechanisms</u>

Biosphere: ozone layer – depletion/elevated skin cancer

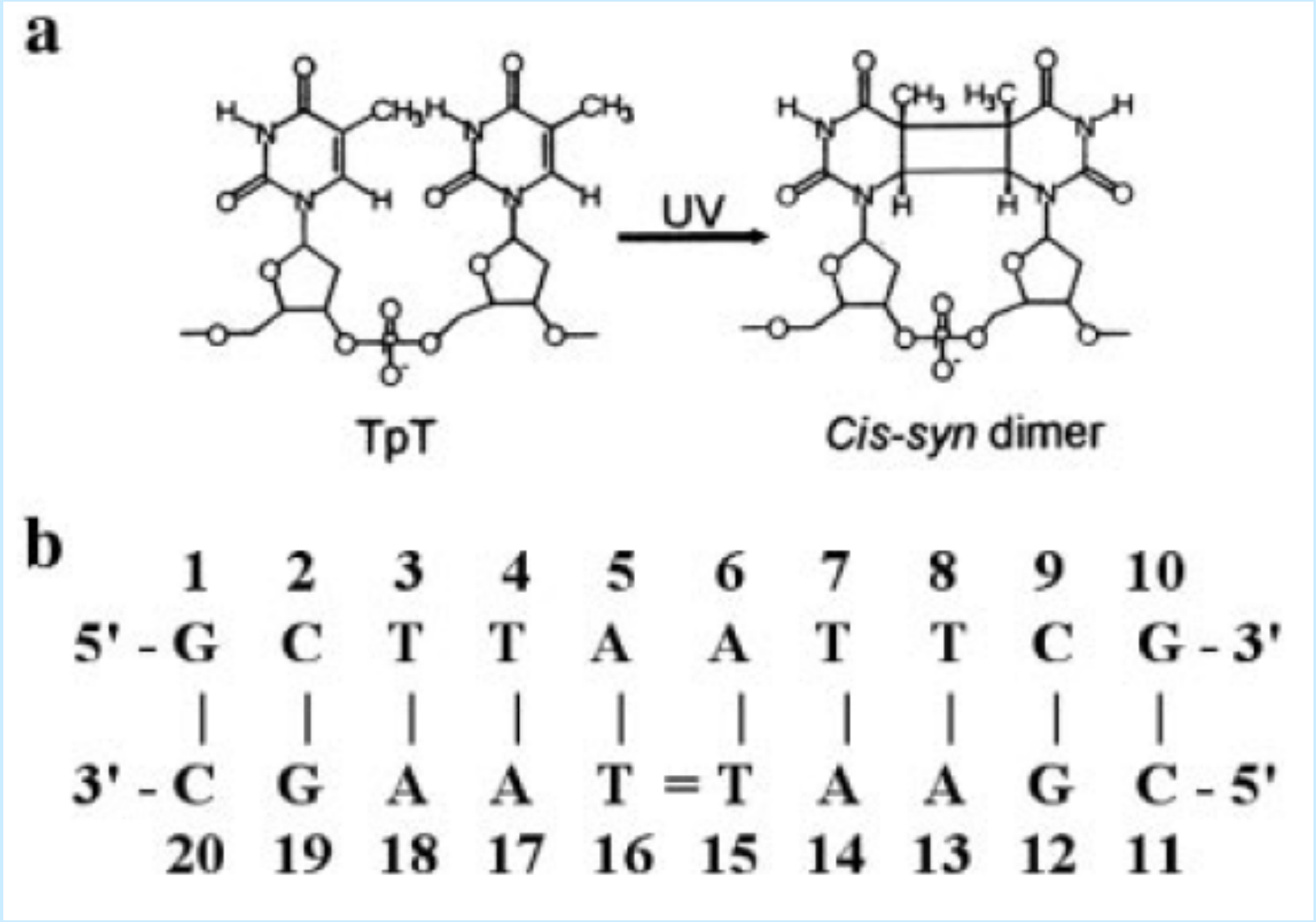
Skin: epidermis cell sloughing of damaged cells

Cells: DNA repair of cancerous genotype

DNA Repair of UV Radiation Damage

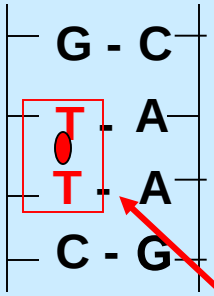


UV Solar radiation damage to DNA

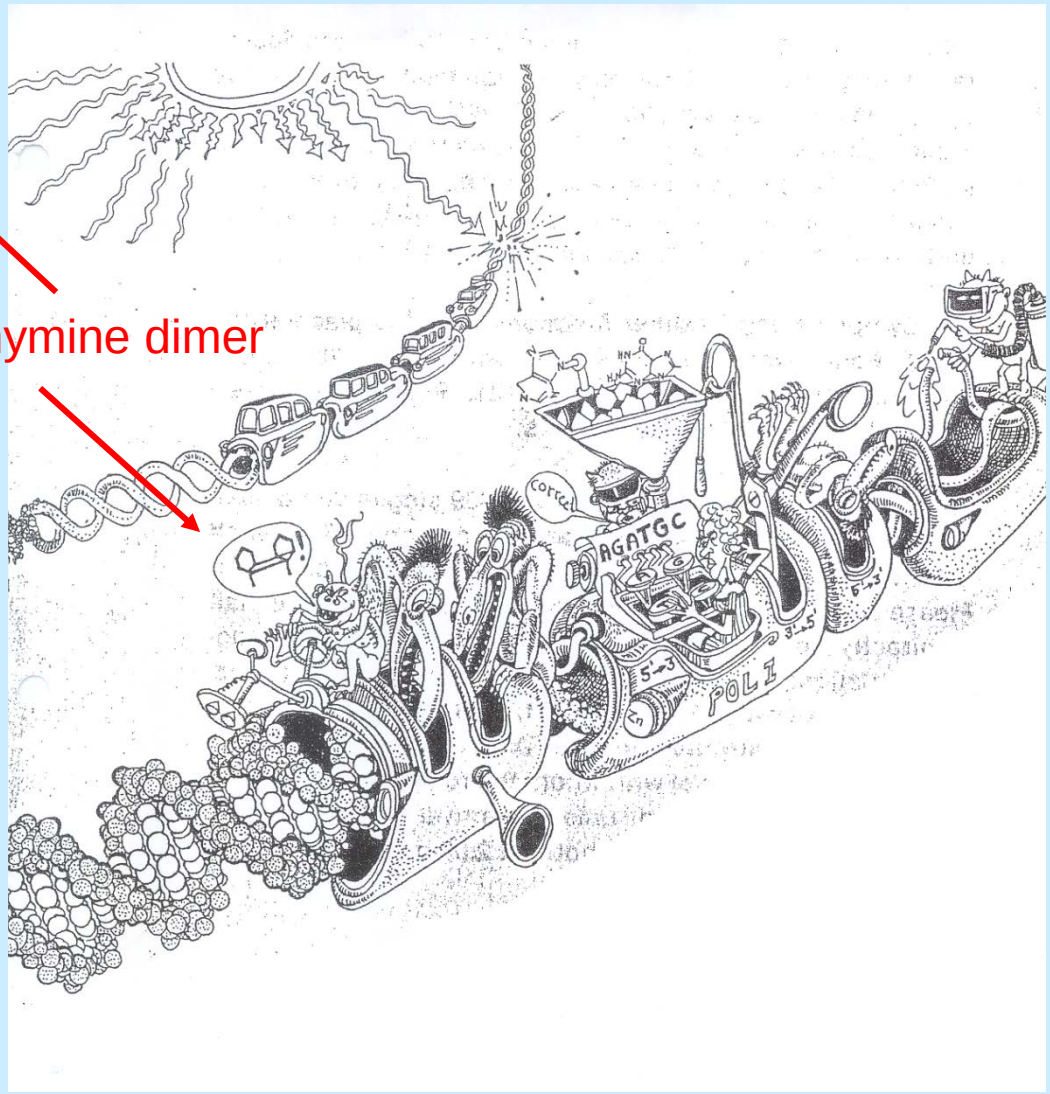


H. Park, et al. Crystal structure of a DNA decamer containing a cis-syn thymine dimer, Proc. Natl. Acad. Sci. USA, 99, 15965 (2002)

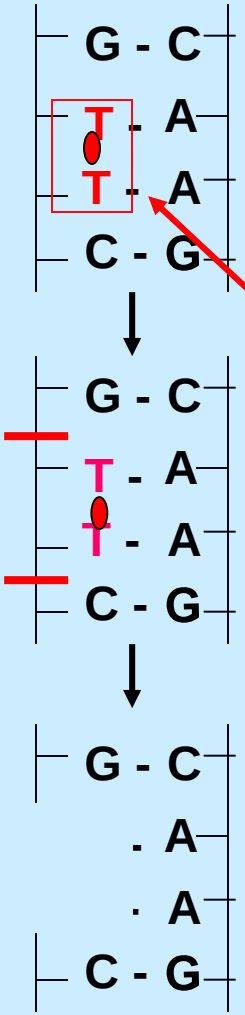
DNA Repair of UV Radiation Damage



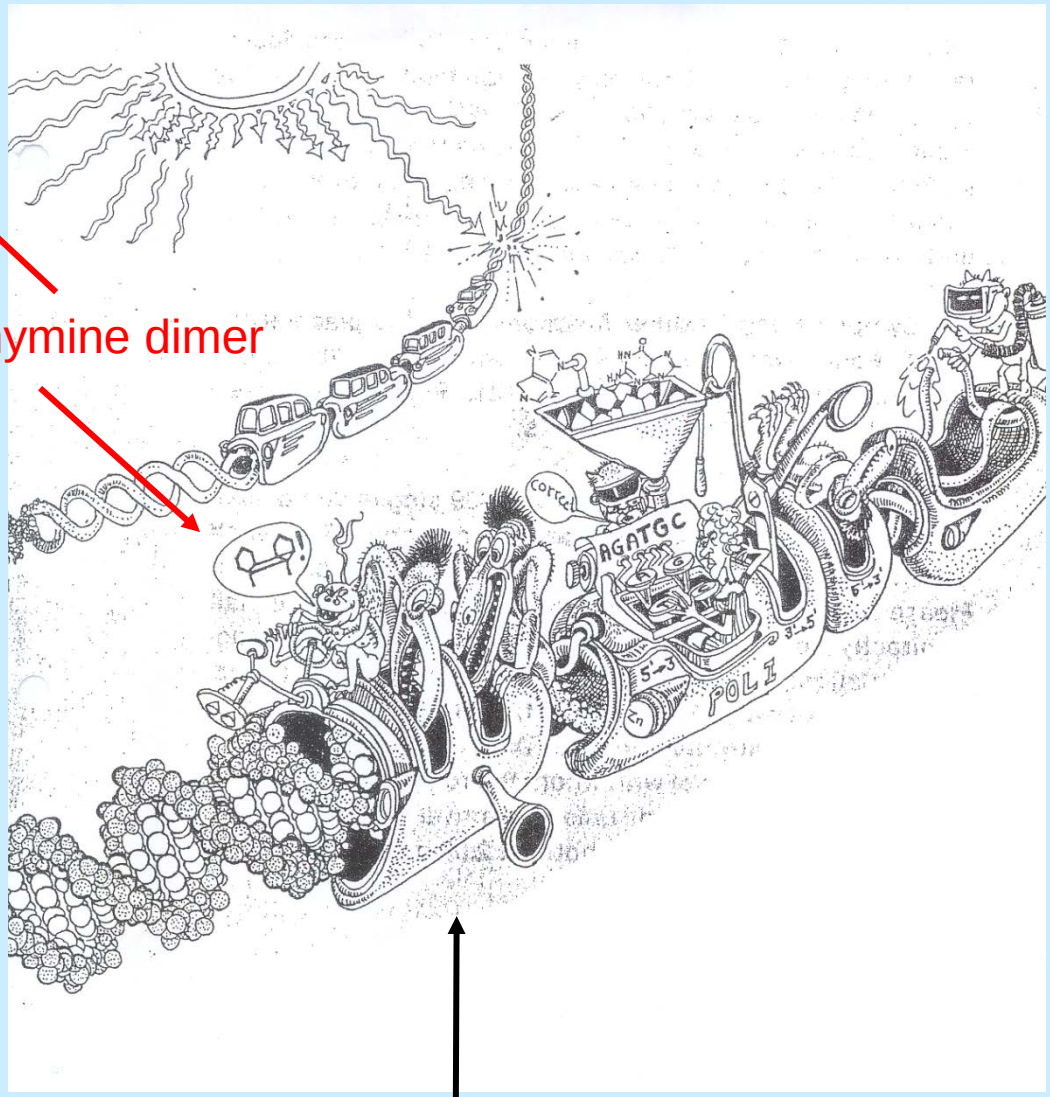
Thymine dimer



DNA Repair of UV Radiation Damage

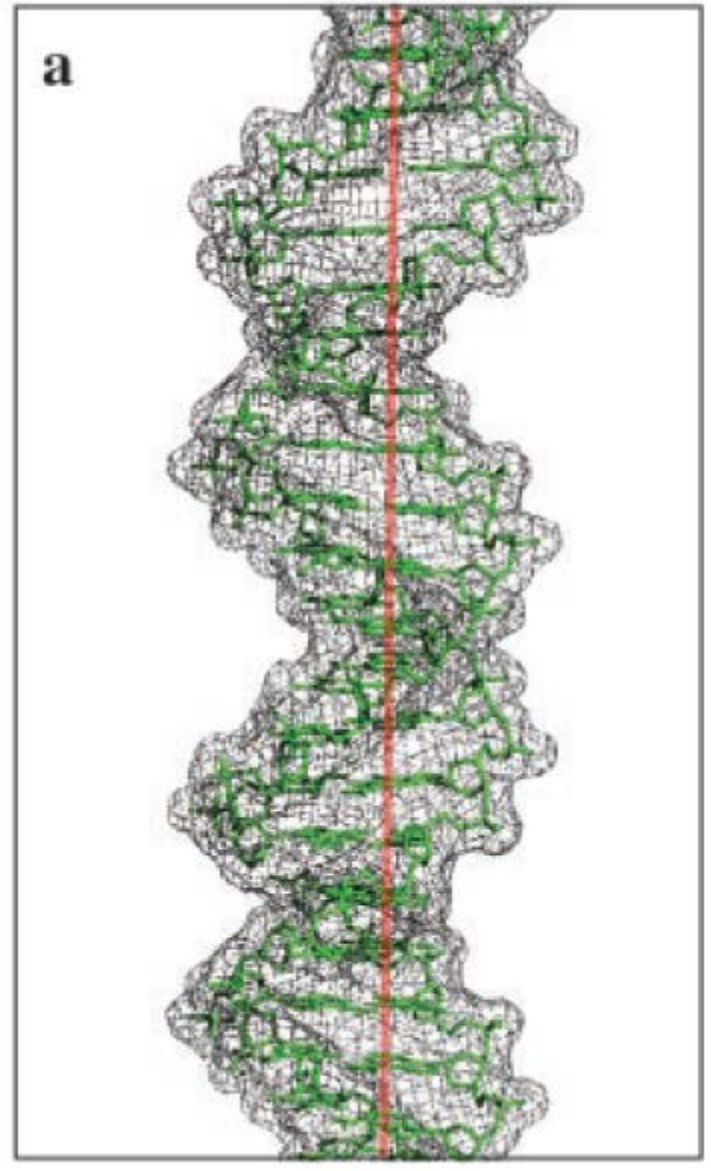


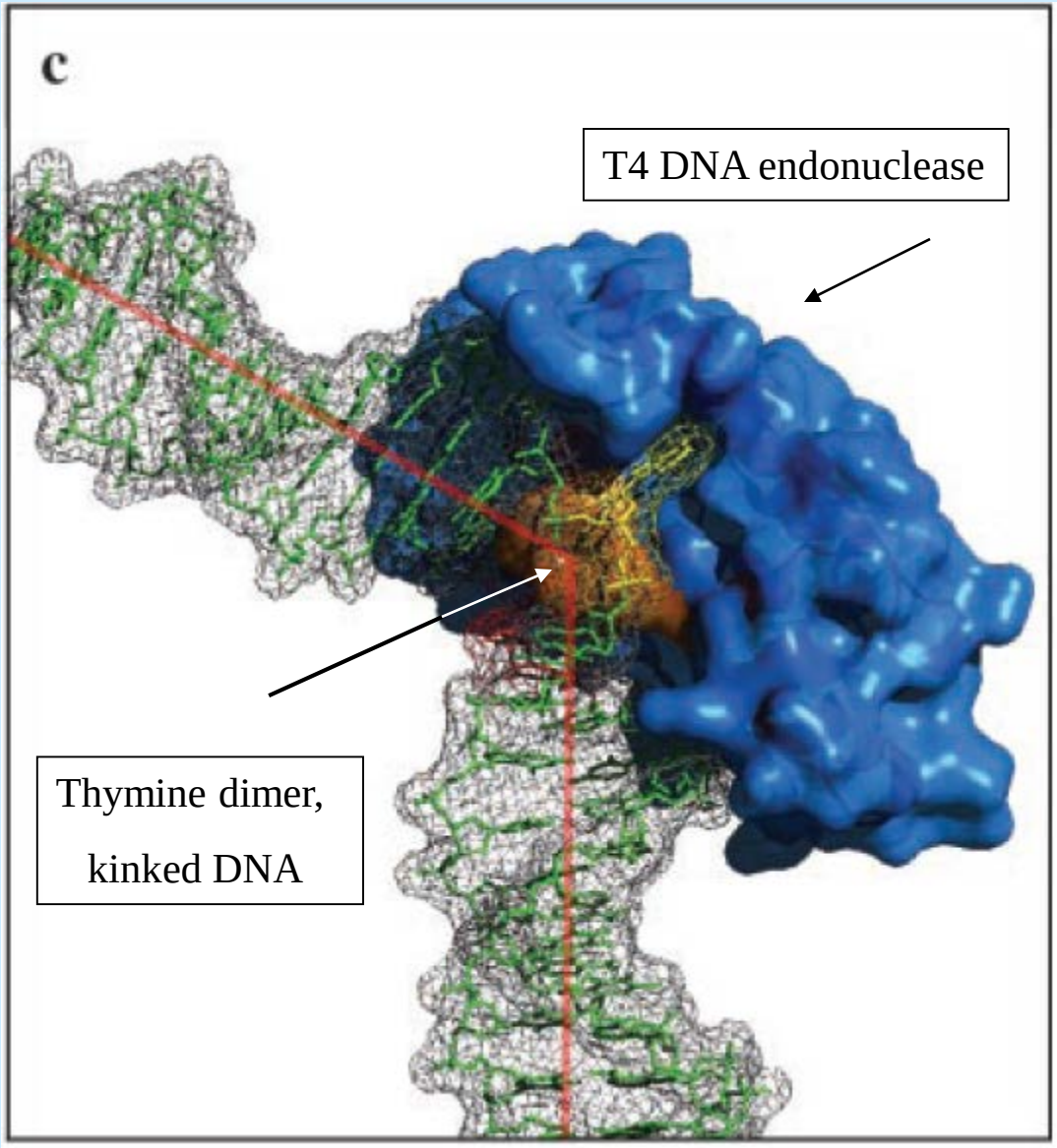
Thymine dimer



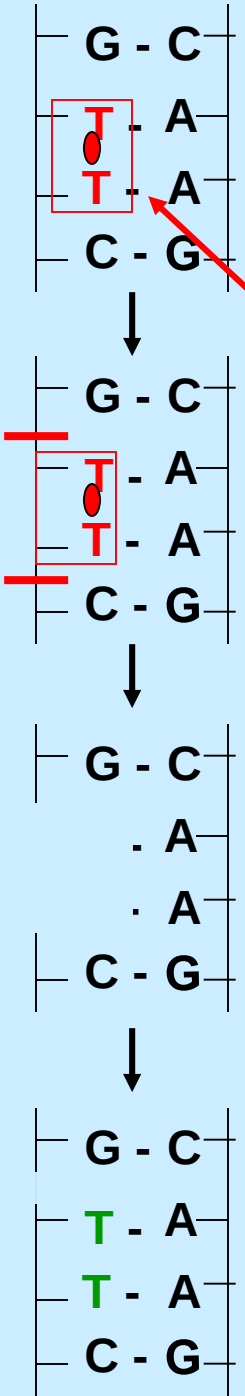
DNA helicase and endonuclease

UV Solar radiation damage to DNA

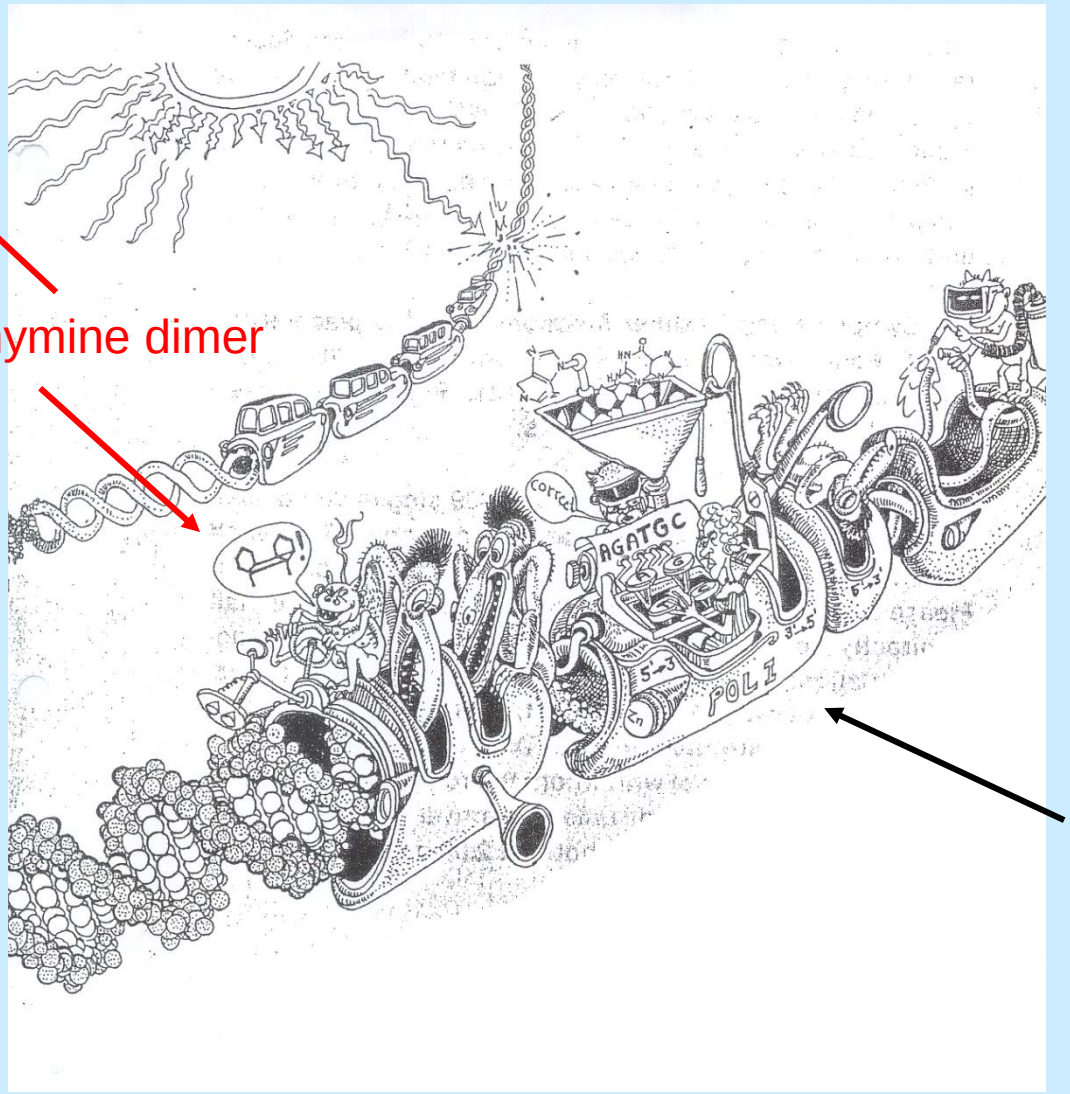




DNA Repair of UV Radiation Damage

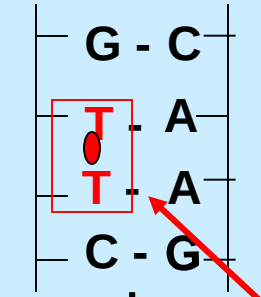


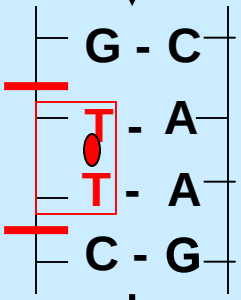
Thymine dimer

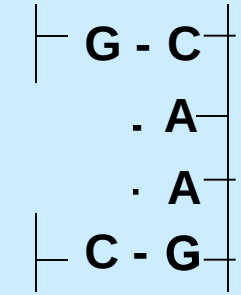


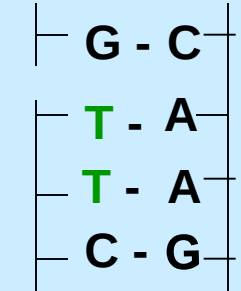
DNA polymerase

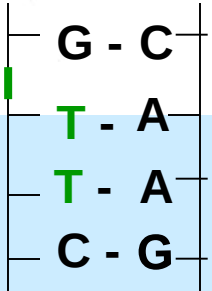
DNA Repair of UV Radiation Damage



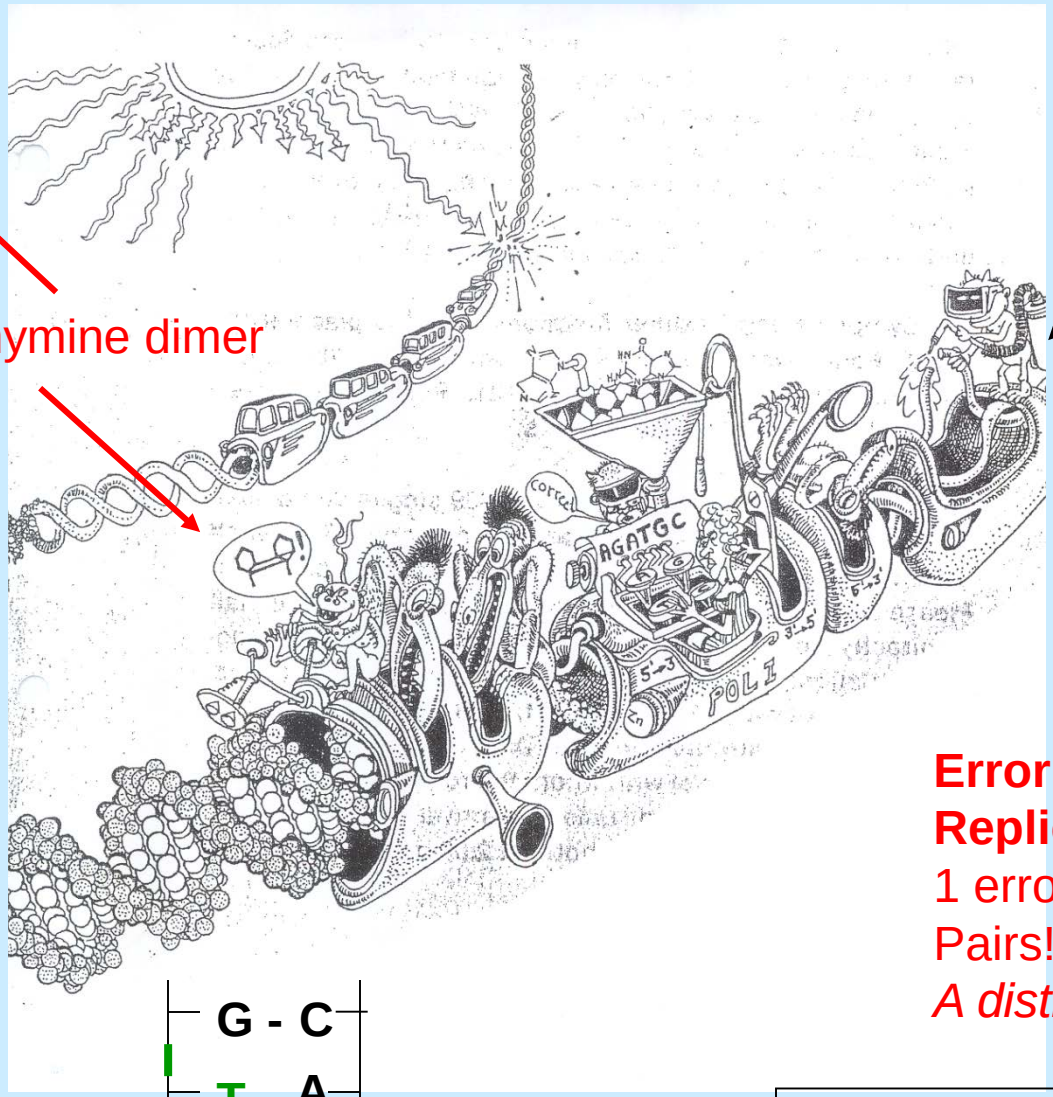








Thymine dimer

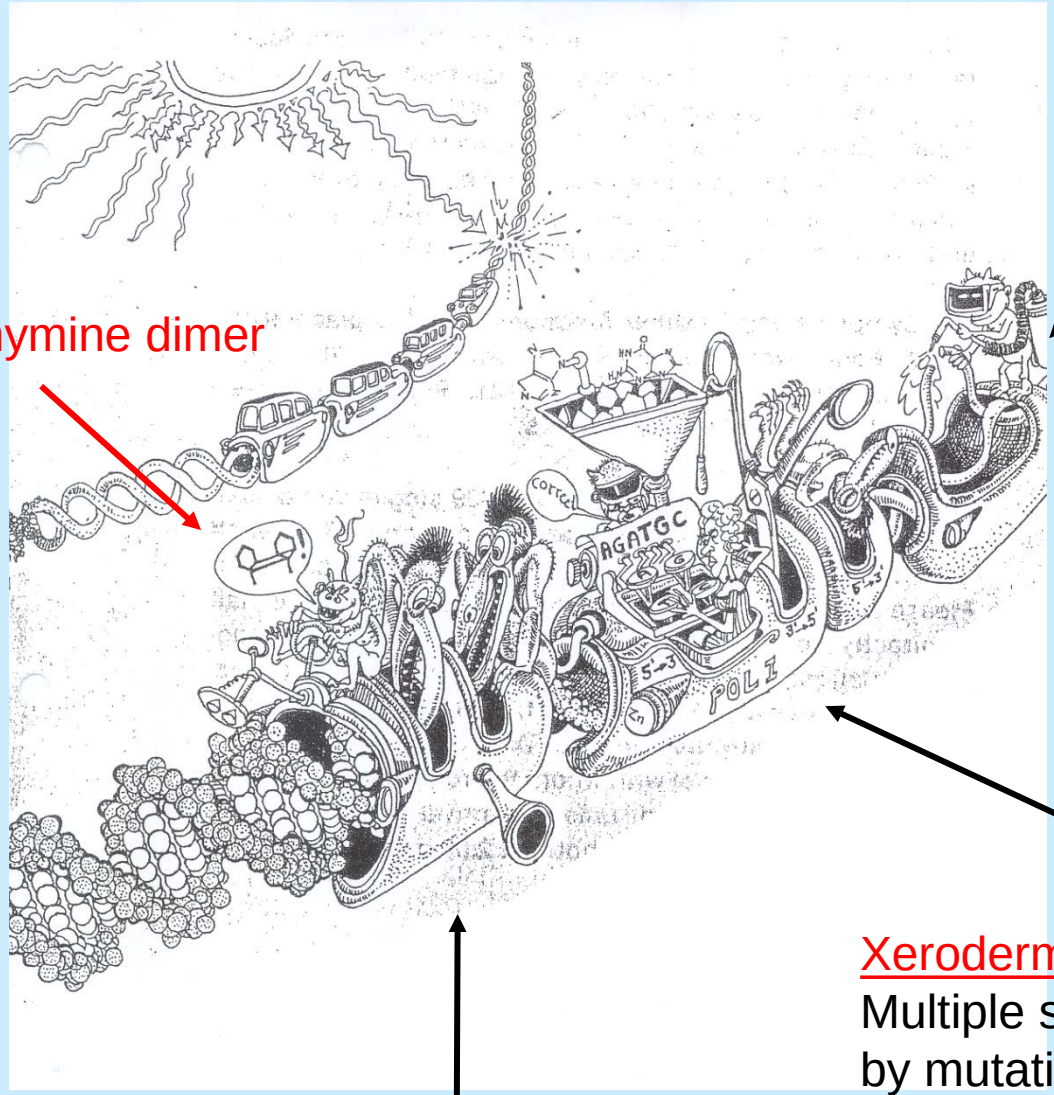


DNA ligase

Error rate for DNA Replication:
1 error/10^{10} base Pairs!
A distributive result.

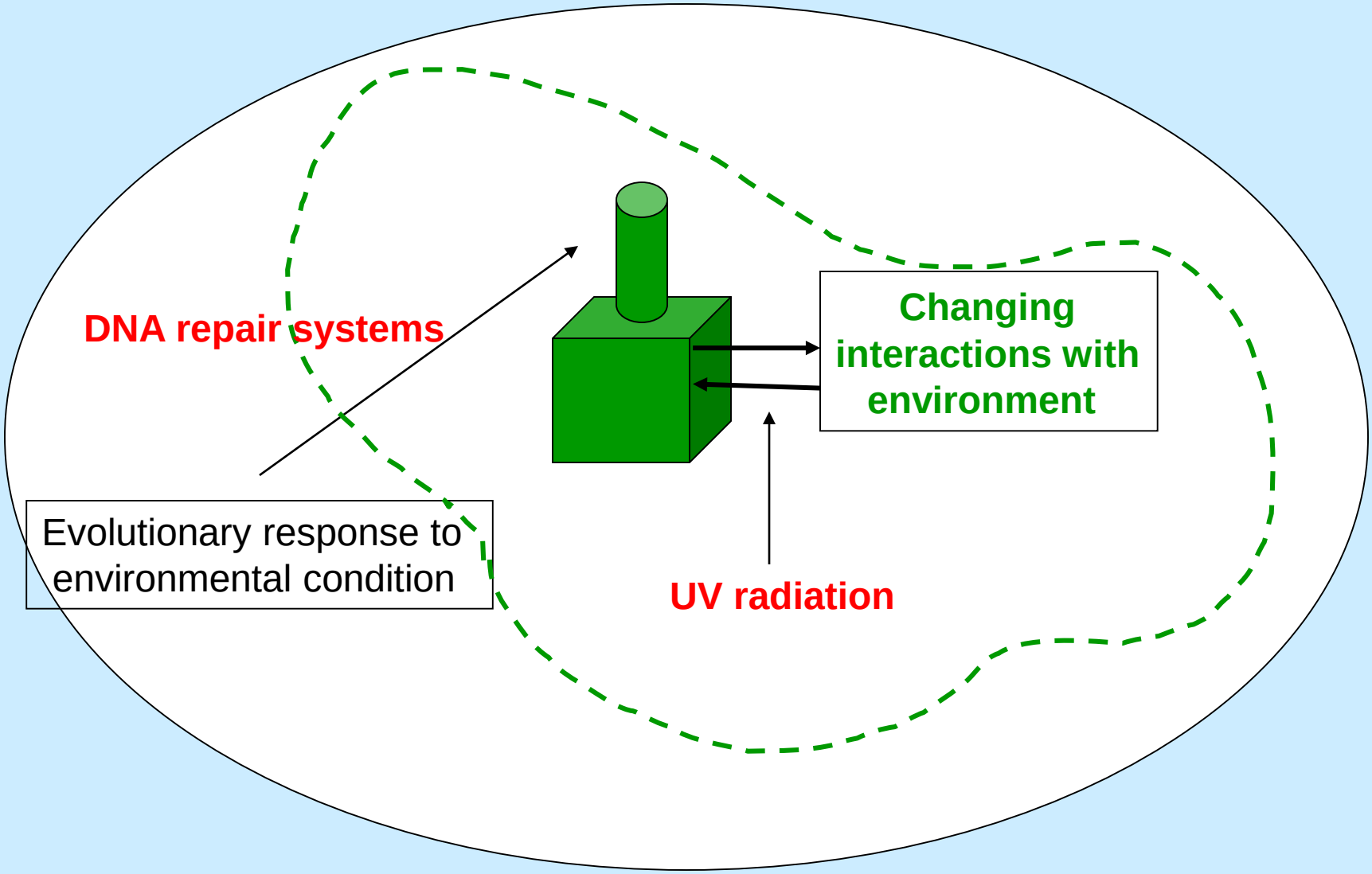
$1/10^{2-3}$	base pairing
$1/10^{4}$	DNA polymerase selection
$1/10^{3-4}$	DNA repair

DNA Repair of UV Radiation Damage

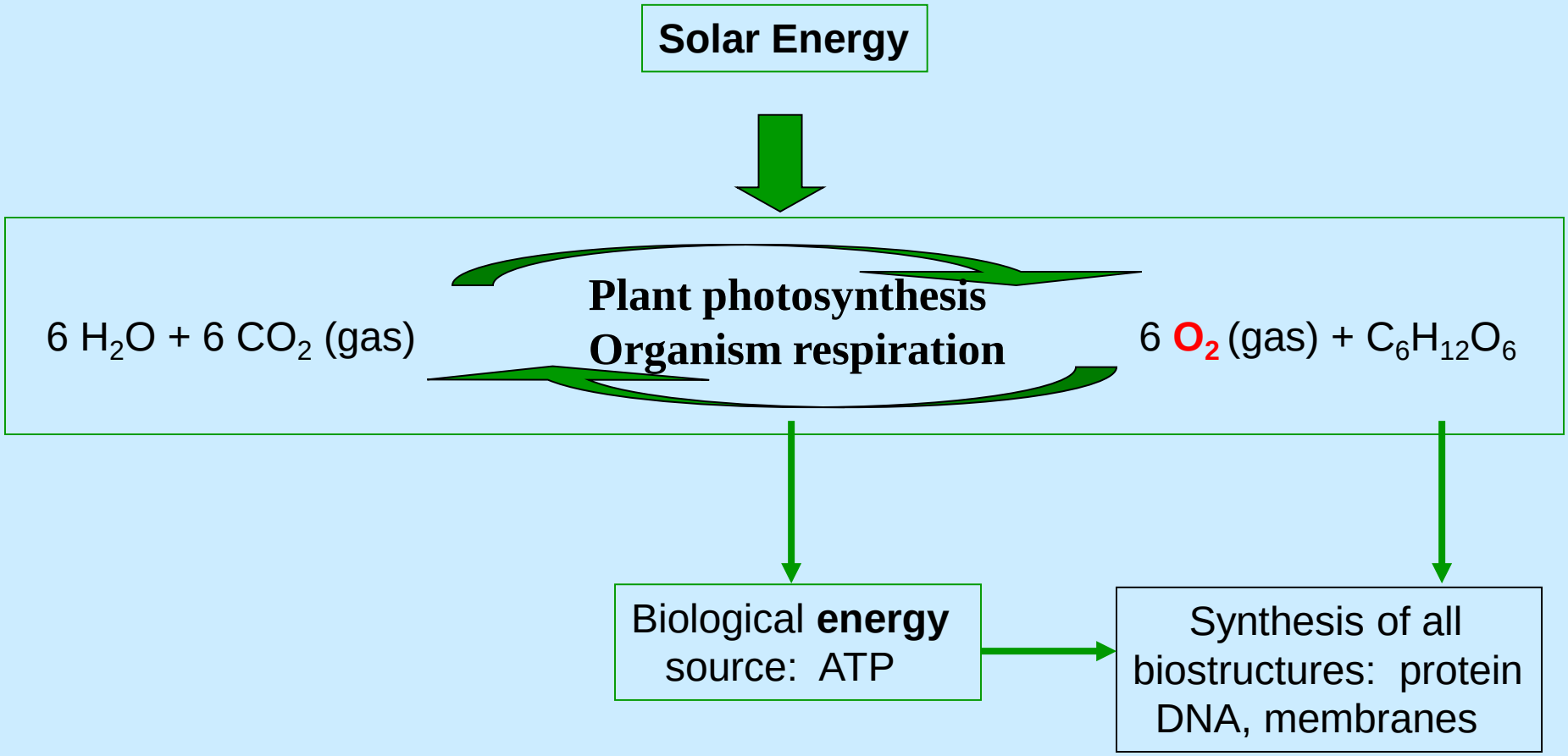


Xeroderma Pigmentosum
Multiple skin cancers caused by mutations in enzymes involved in repair of UV damage to DNA

Organisms and the Environment: Evolutionary Implications



Fitness: organism lives successfully within an environmental context.



Oxygen is our life line but …

Organismic Adaptations within the Environment

Fresh air
Oxygen!

Organismic Adaptations within the Environment

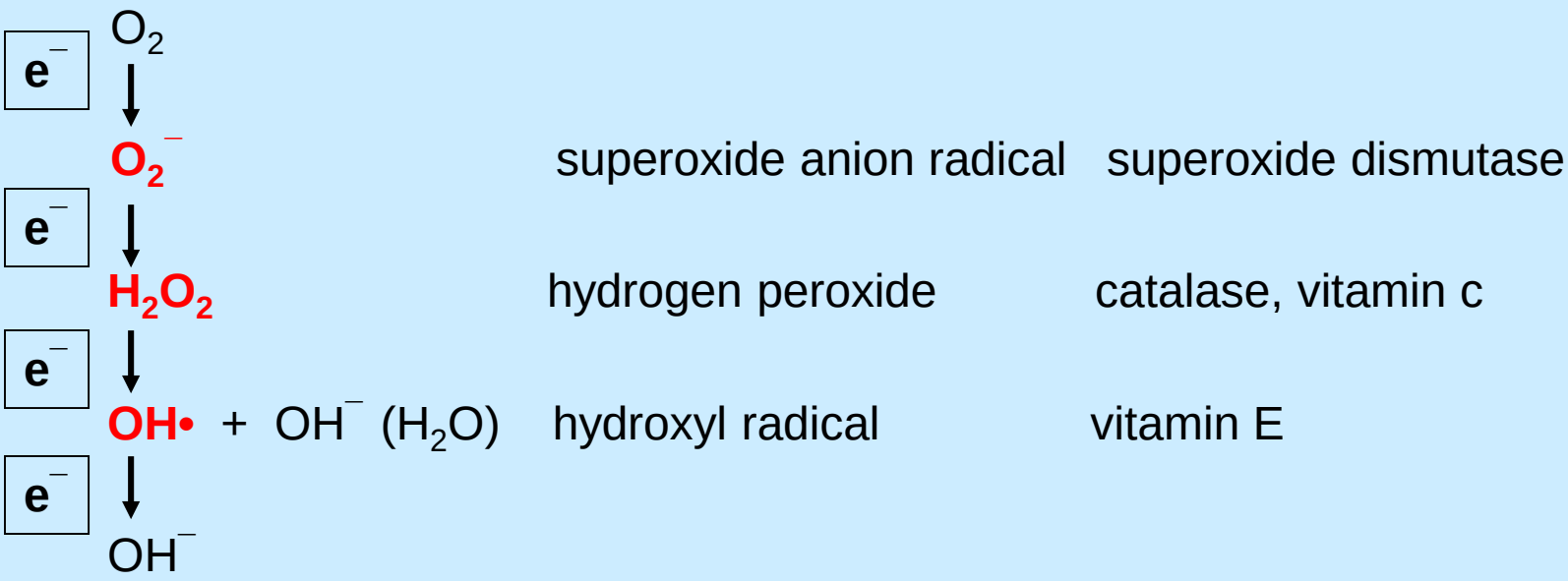
Fresh air
Oxygen!
Oxygen is toxic

Organismic Adaptations within the Environment

Fresh air
Oxygen!
Oxygen is toxic

Lung: anti-oxidants
Cells: protection against reactive oxygen species
DNA repair: 10^4 -10^5 G base/cell/day

Reactive Oxygen Species



Our lungs are adapted to an oxygen-containing atmosphere.
But …

Guanine (DNA base)	$\xrightarrow{OH\bullet}$	8-hydroxyguanine (mutation)

DNA Damage from Breathing Oxygen

100,000 8-hydroxyguanine bases excreted/day/cell because of DNA repair of O_2 damage

or 10^5 8-hydroxyguanine bases excreted/day/cell

Is this meaningful to anyone?

Try this calculation.

How many 8-hydroxyguanine bases are excreted per cell in a lifetime (80 years) and how does that number relate to the total number of guanine bases in your DNA (your chromosomes; your genome)?

Basic equation: two equal proportions–A is to B as C is to D

10^5 8-hydroxyguanine bases excreted/day/cell = X/80 years/cell = X/365 days/cell

Y

Solve for X

$$X = \frac{10^5 \text{ 8-hydroxyguanine bases excreted}}{1 \text{ day}} \times 80 \text{ years/cell} \times \frac{365 \text{ days}}{1 \text{ year}} = \mathbf{2.92 \times 10^9}$$

8-hydroxyguanines

(units conversion: factor of 1)

$$(10^5 \text{ 8-OH-G/cell/day}) \times (3.65 \times 10^2 \text{ days/yr}) \times (8 \times 10^1 \text{ yr/lifetime})$$

There are about 5,000,000,000 bases in the human genome (2.5×10^9 base pairs–AT and GC)
On the average there are similar amounts of each base in the genome, so there are about **1.2×10^9 guanines/genome**.

Compare the number of damaged guanine bases over a lifetime with the total number of guanines in the genome:

2.92×10^9 8-hydroxyguanines vs. **1.2×10^9 guanines/genome**.

One the average every guanine base is damage about 2.5 times over a person's lifetime.

Without repair, damage would lead to mutation and cancer. With repair, we continue to enjoy breathing fresh air.

There are 6×10^{23} molecules per mole (1 mole = 1 gram molecular weight).
1×10^{19} molecules/6×10^{23} molecules/mole = 1.7×10^{-5} moles or 17 micromoles

In this case, the gram molecular weight of hydroxy-guanine is 153 grams/mole. So, the weight of 8-hydroxy-guanine that is present in urine each day is about…

$(1 \times 10^{19}$ hydroxyguanine/day/body) x (1 mole/6×10^{23} molecules) x (153 grams/mole) = 2.6×10^{-3} grams or 2.6×10^{-3} grams x 10^{3} mg/gram = 2.6 mg hydroxyguanine excreted per day or 2600 micrograms.

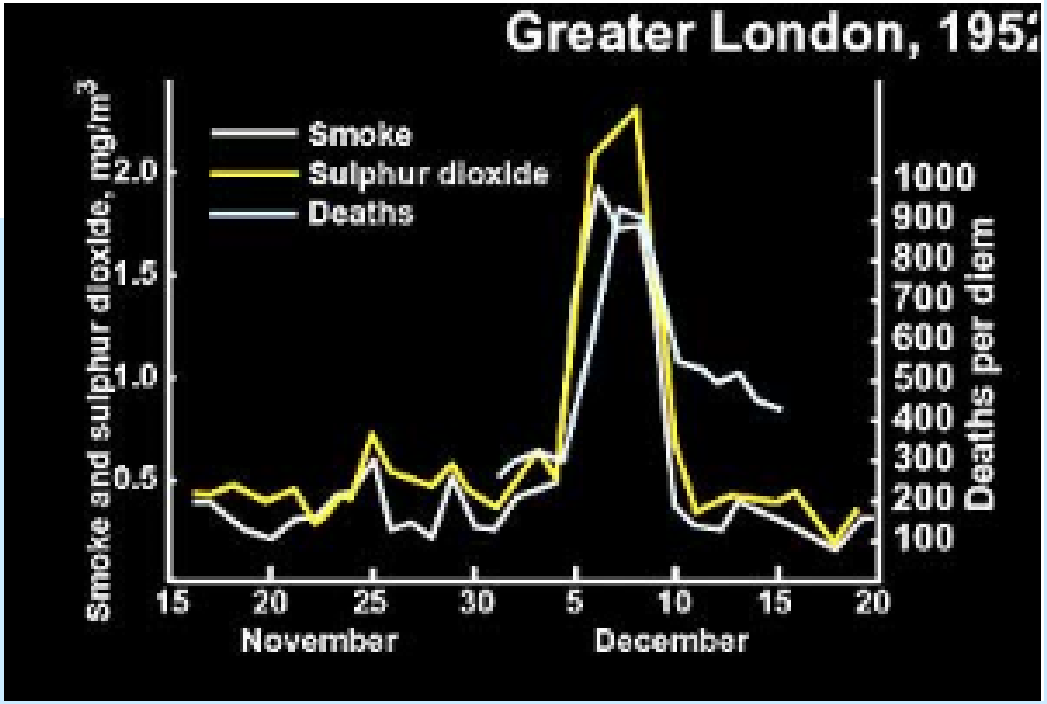
Where/how does the cell get the replacement guanine?

What happens when an air pollution load is imposed on this background?
8-hG excretion increases from 10^{5}/cell to 10^{6} - 10^{7}/cell

Can repair systems keep up with increased load?

London, England: Weather inversion in 1948

Perhaps as many as 12,000 people died!



http://www.npr.org/programs/atc/features/2002/dec/londonfog/lioygraphic.html

Entrance to Forbidden City in Beijing China on a clear day!

Problem: our lungs are not adapted to this chronic level of air pollution.

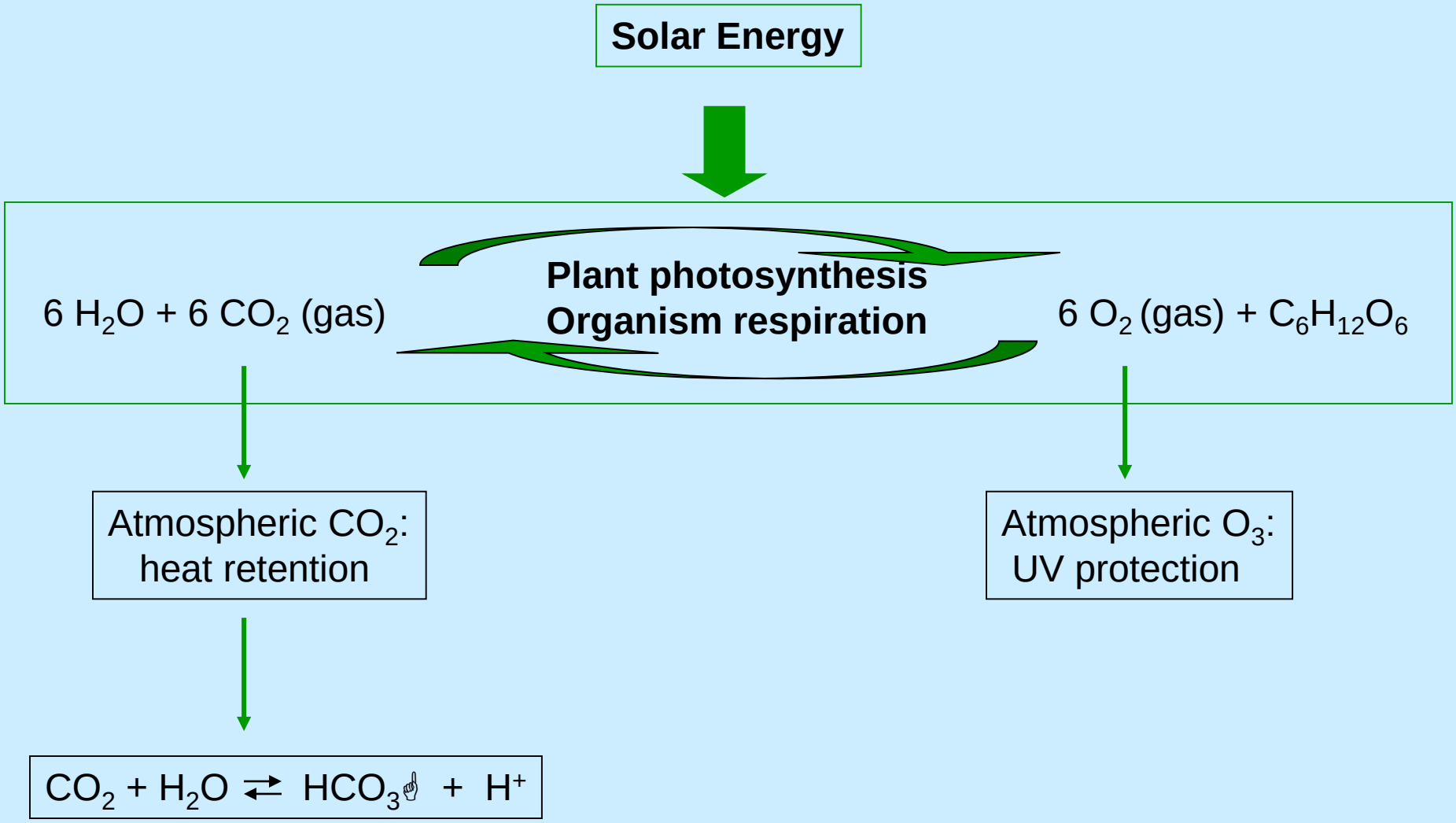
Entrance to Forbidden City in Beijing China on a clear day!

Problem: our lungs are not adapted to this chronic level of air pollution. Short term protective measures (inflammation) cause long term lung injury as side effect of digesting foreign agents in the lung.

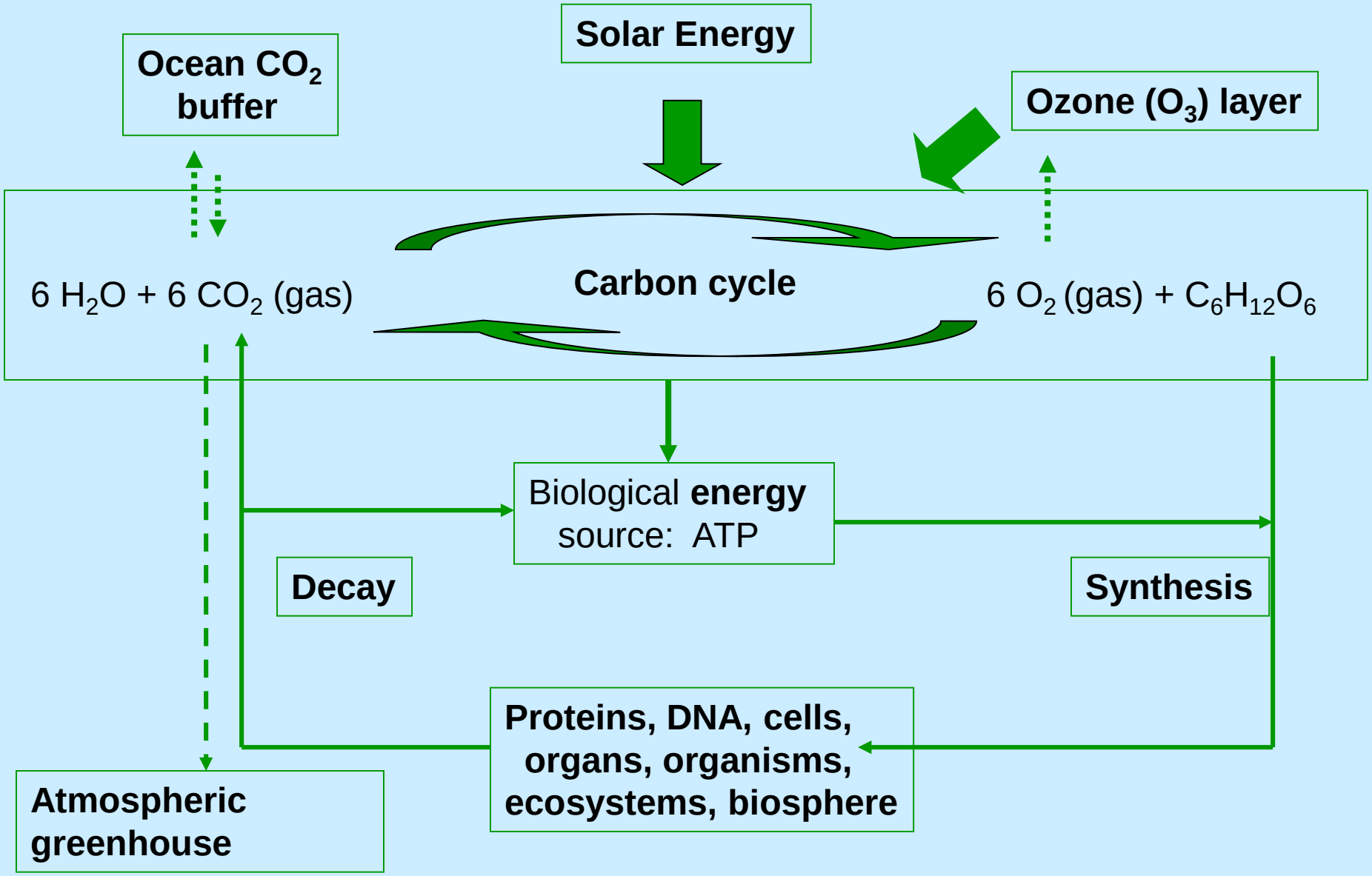
Implications for the environment and human health of the discovery and domestication of fossil hydrocarbons

ENERGY!

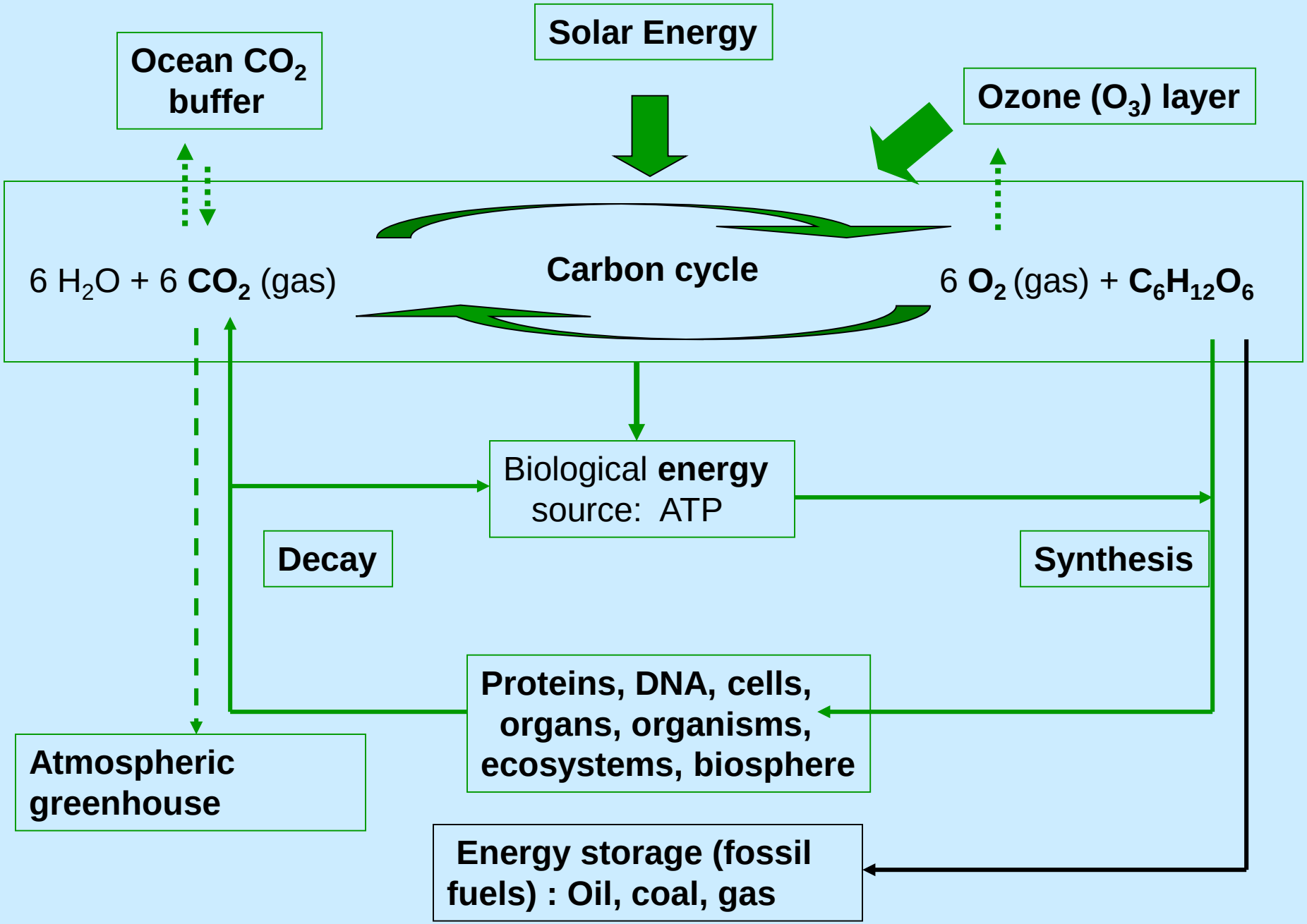
From solar to fossil… and back again?



Photosynthesis and respiration at the biospheric level.
Basic environmental protections/constraints



The carbon cycle works in the context of a world that a) has a large ocean to store CO_2, b) enough atmospheric CO_2 to keep the biosphere warm, and c) O_2 to provide the starting material for carbohydrate oxidation and ozone formation (O_3).



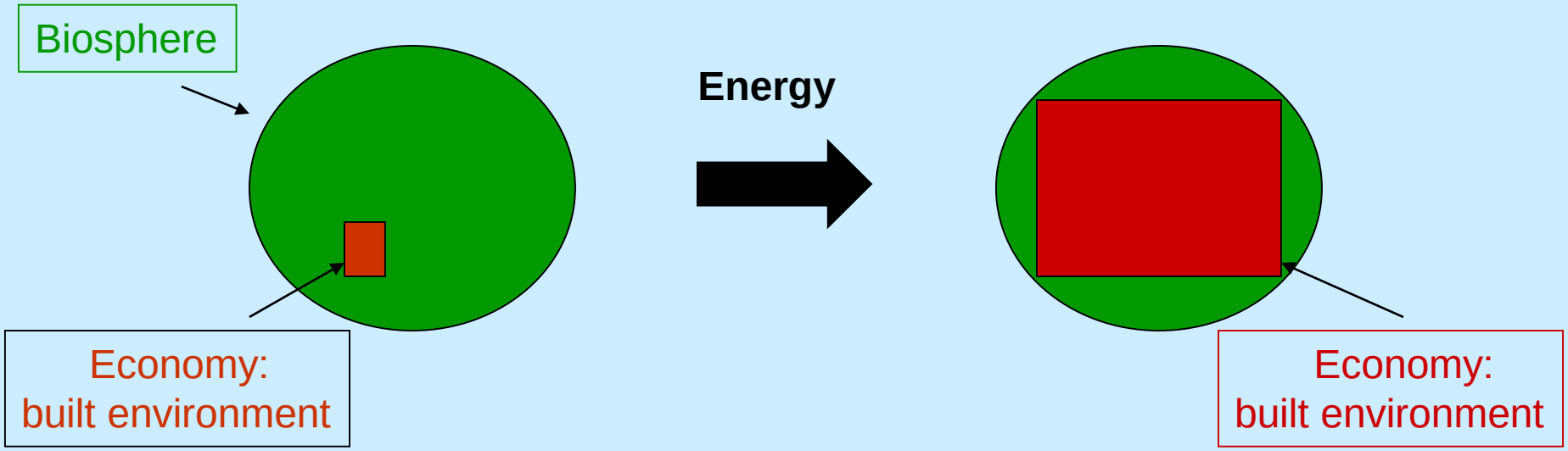
During biological history, solar energy and carbon have been stored.

Human Domination of Earth's Ecosystems

The Issue of Scale

Empty world-1750

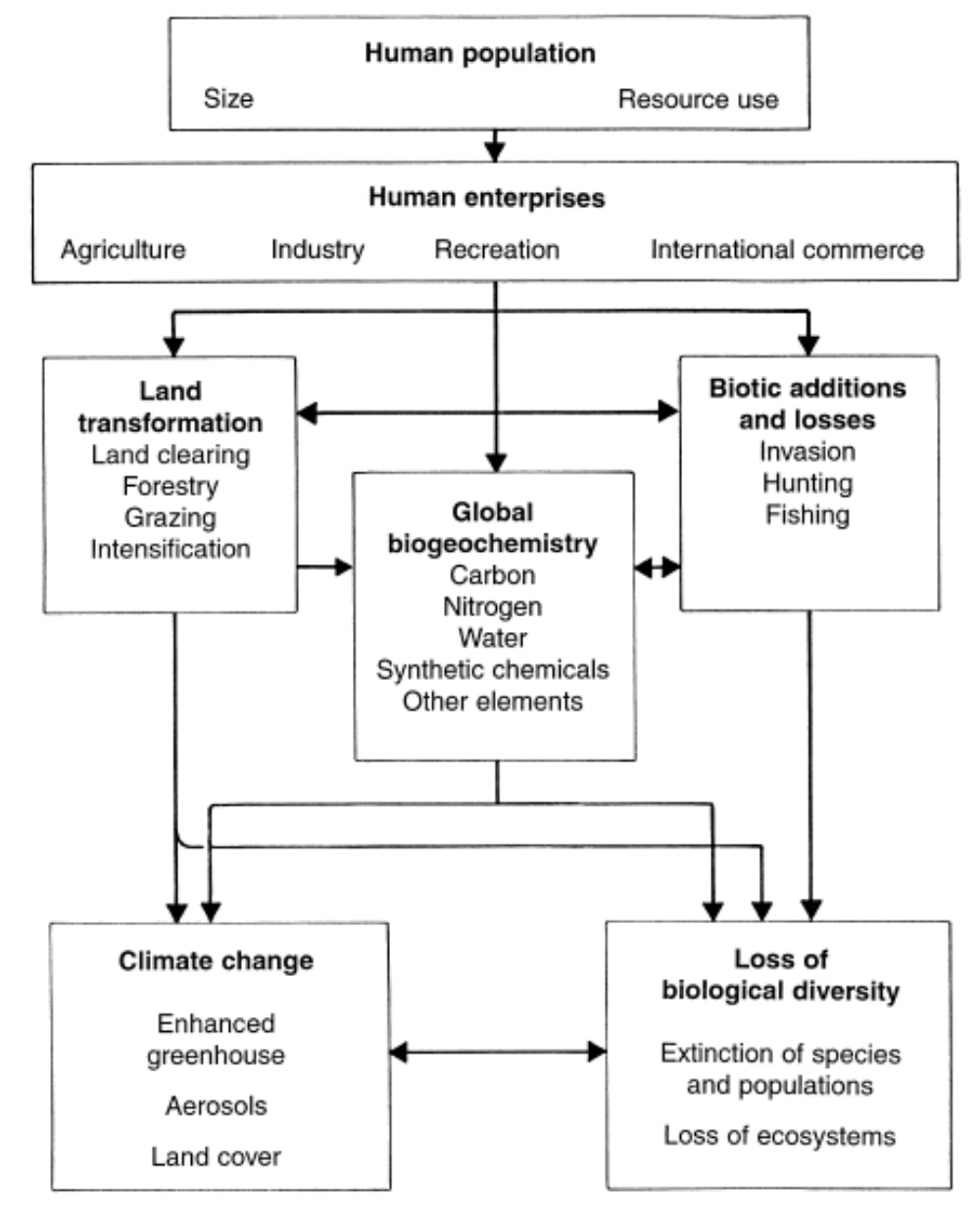
Full world-2100



Herman Daly: Beyond Growth, the Economics of Sustainable Development

Full World: Human Domination of Earth's Ecosystems

PM Vitousek et al Science, 277, 494 (1997)



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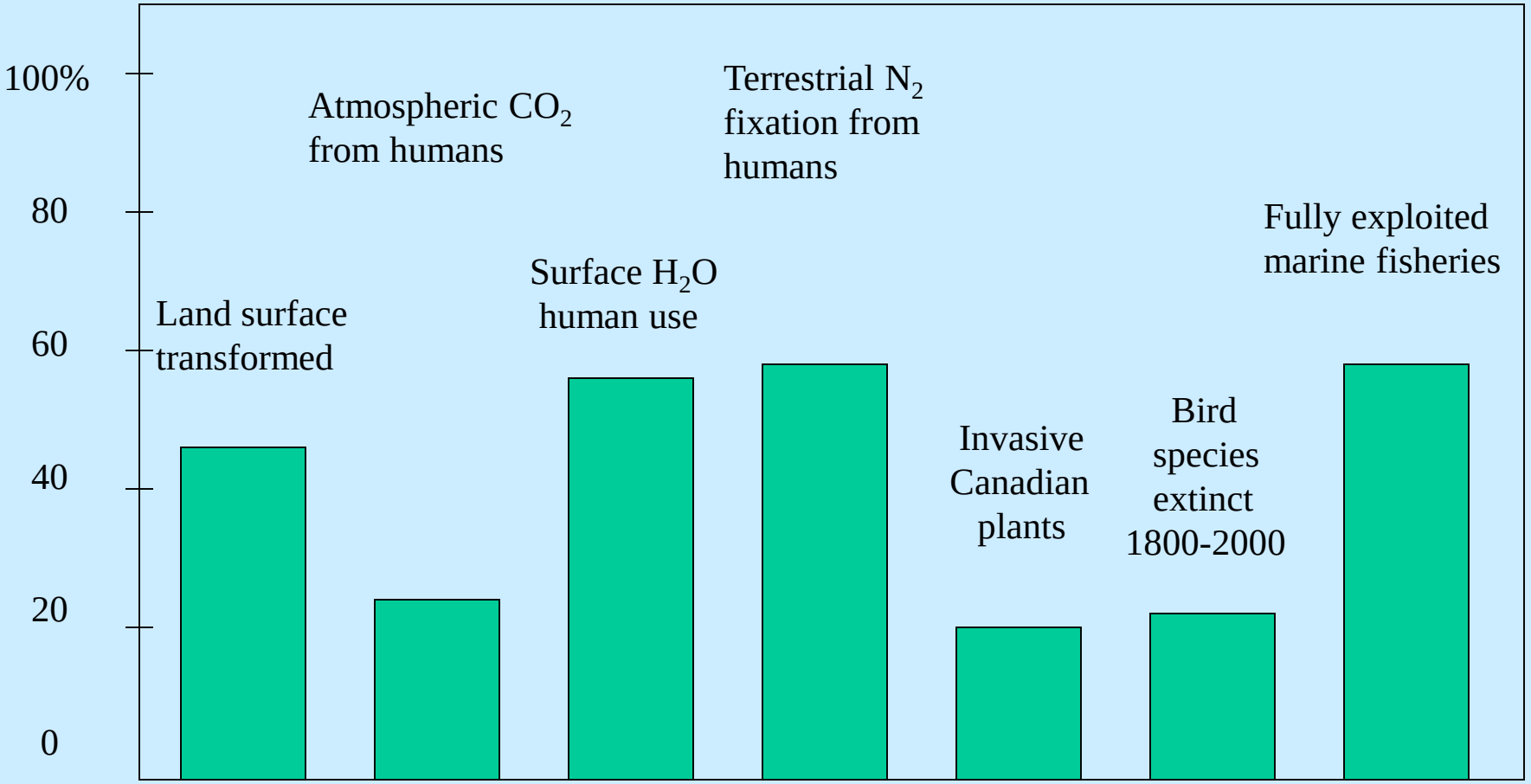

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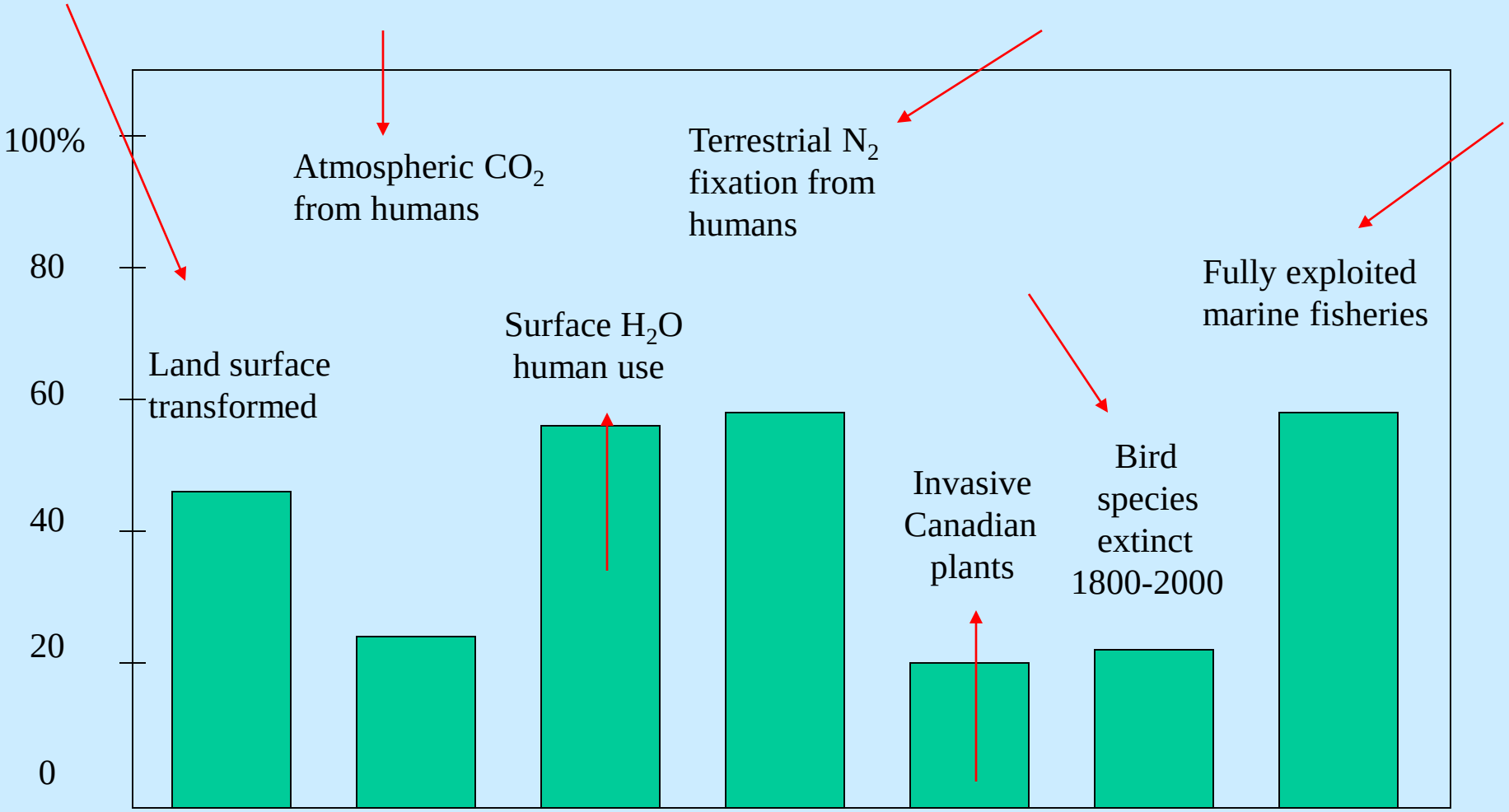
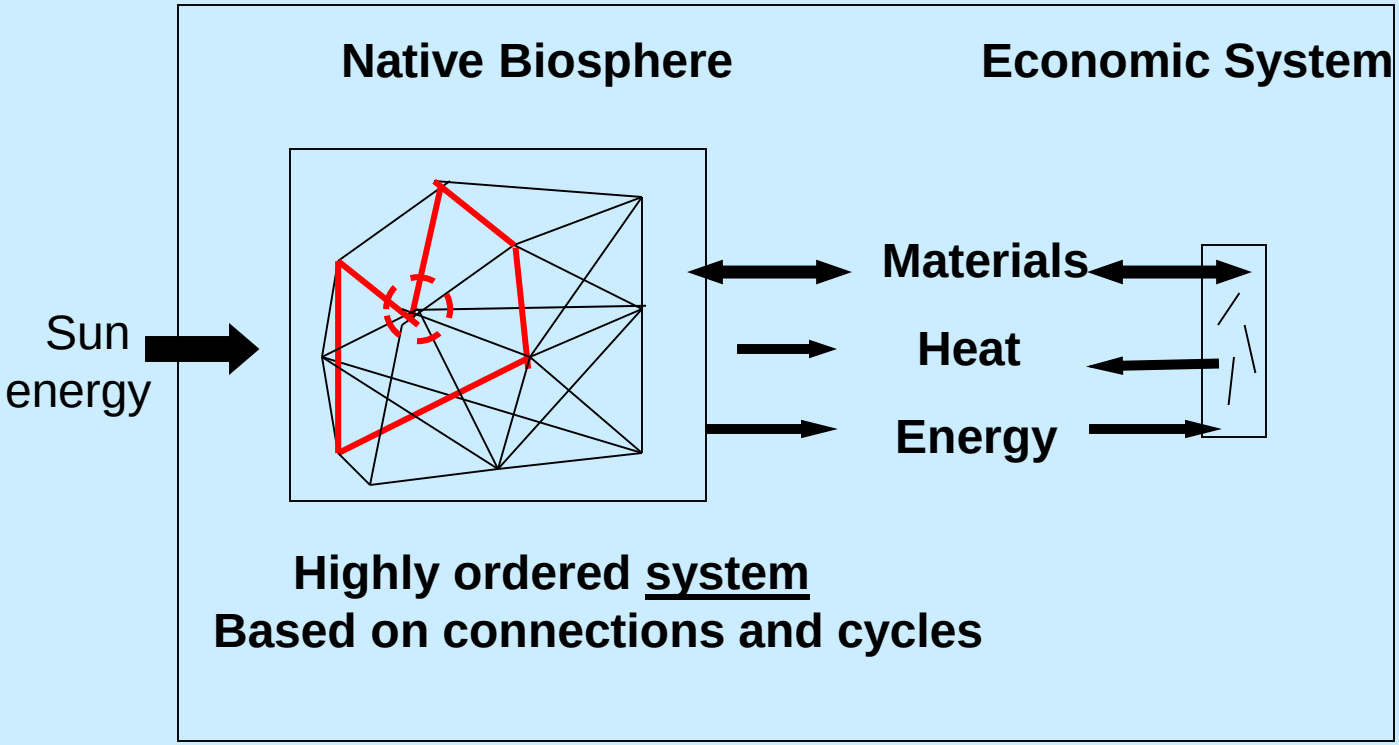


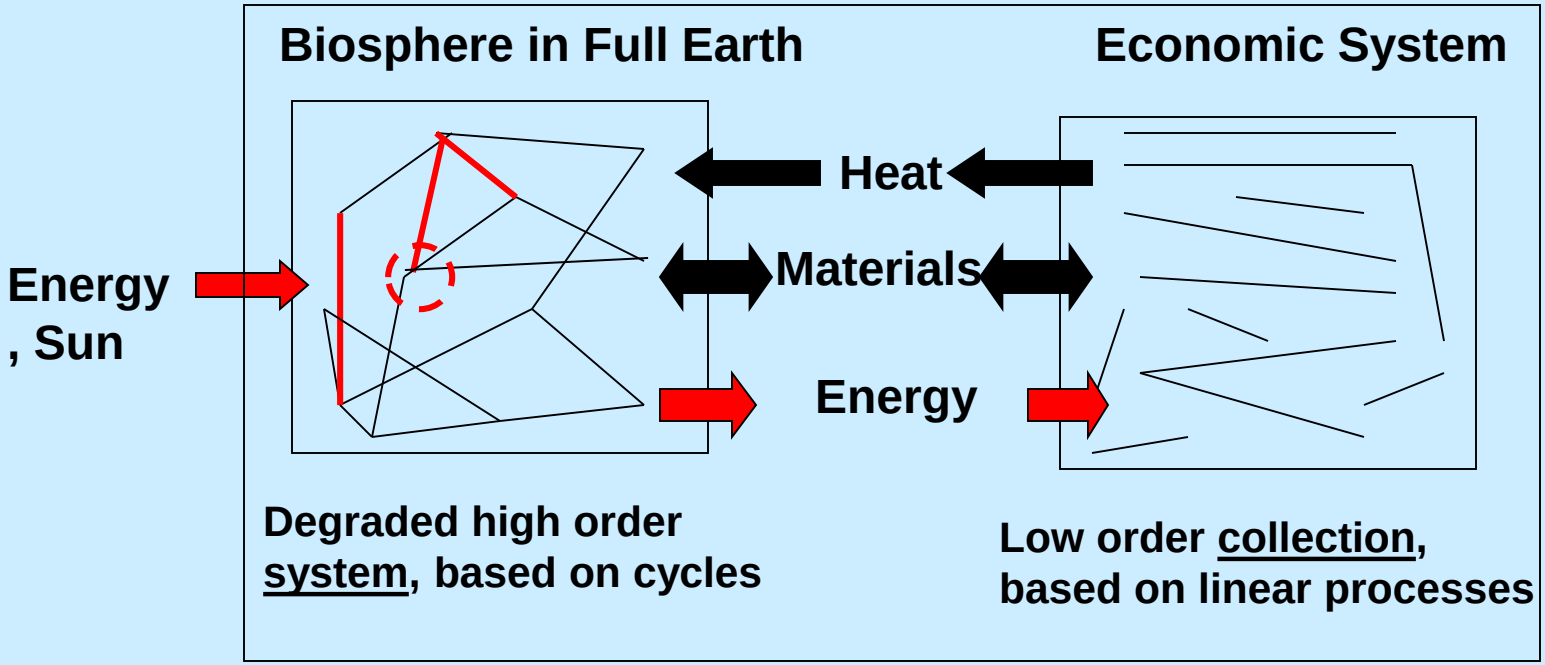
Tragedy of the Commons: Garrett Hardin

The Problem of Scale: Early Industrialized World

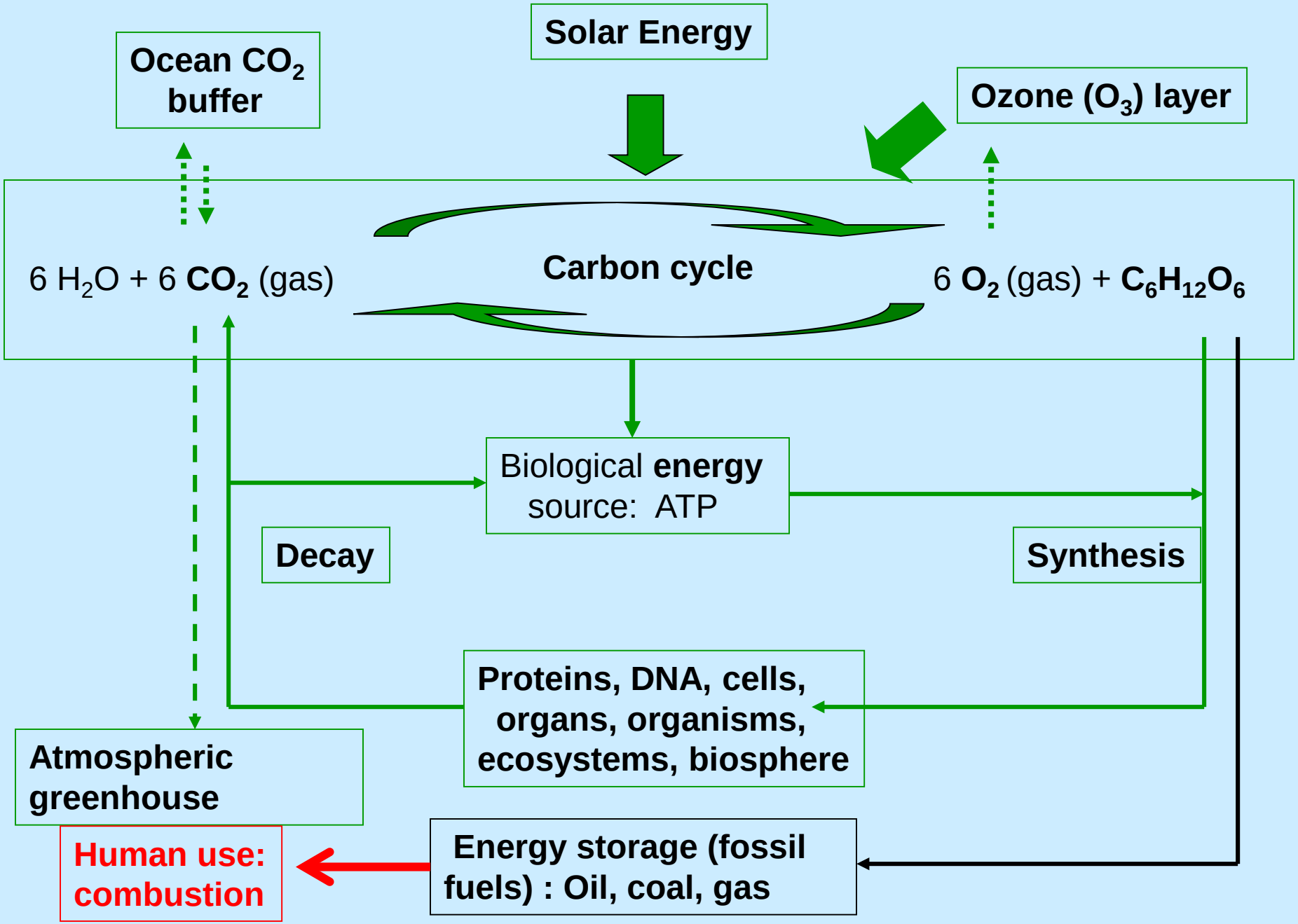


Impact of economic system on ecosystem was small because the economic system was small
(Herman Daly)

The Problem of Scale: Full world



• Economic system is of comparable size to the ecosystem and directly competes with it.
e.g. Nearly 50% of the primary photosynthetic production of the Earth (energy to support biosphere) is diverted to support human activity.
• Products are made and bi-products are generated that are not parts of cycles (recycling)



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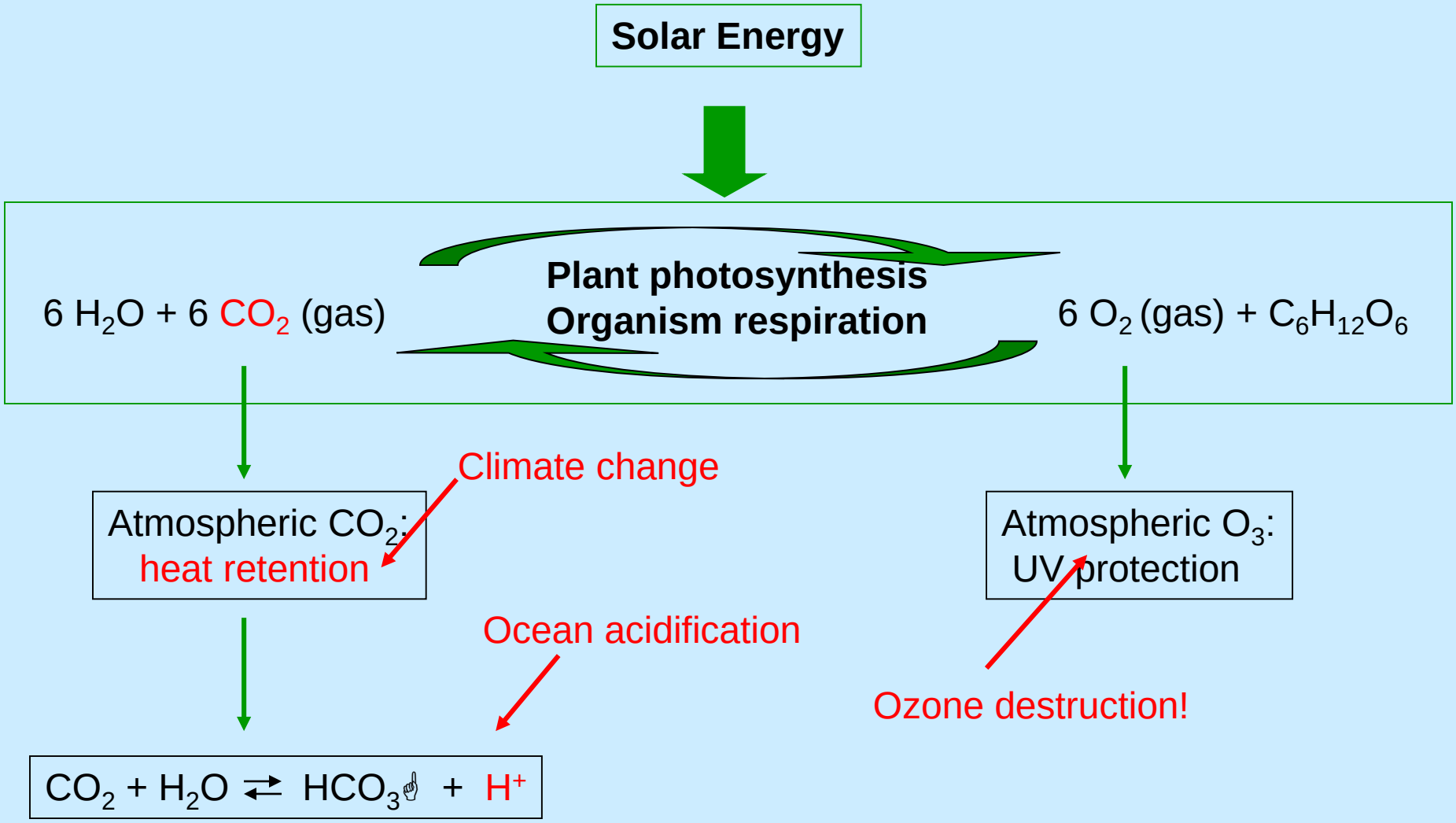
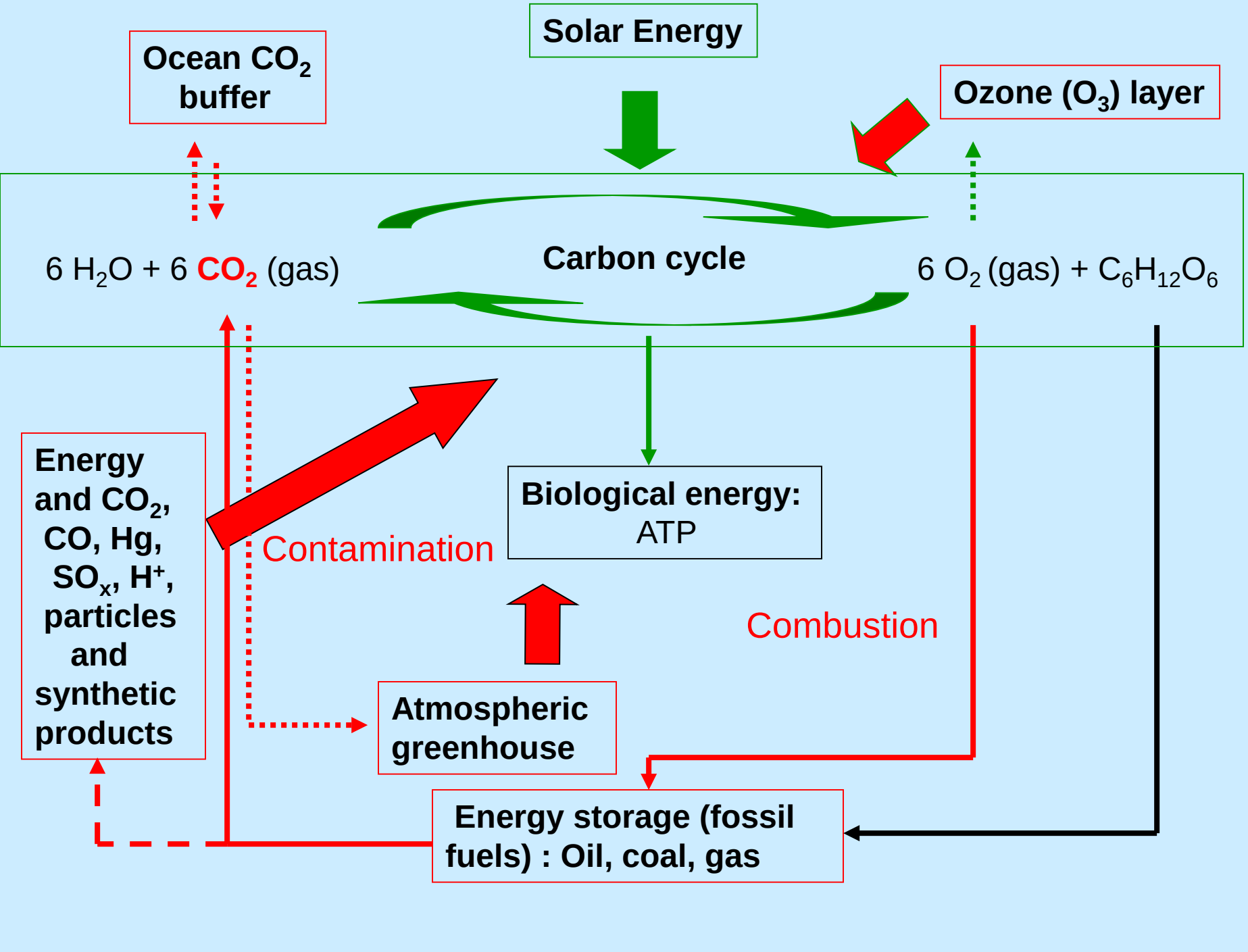
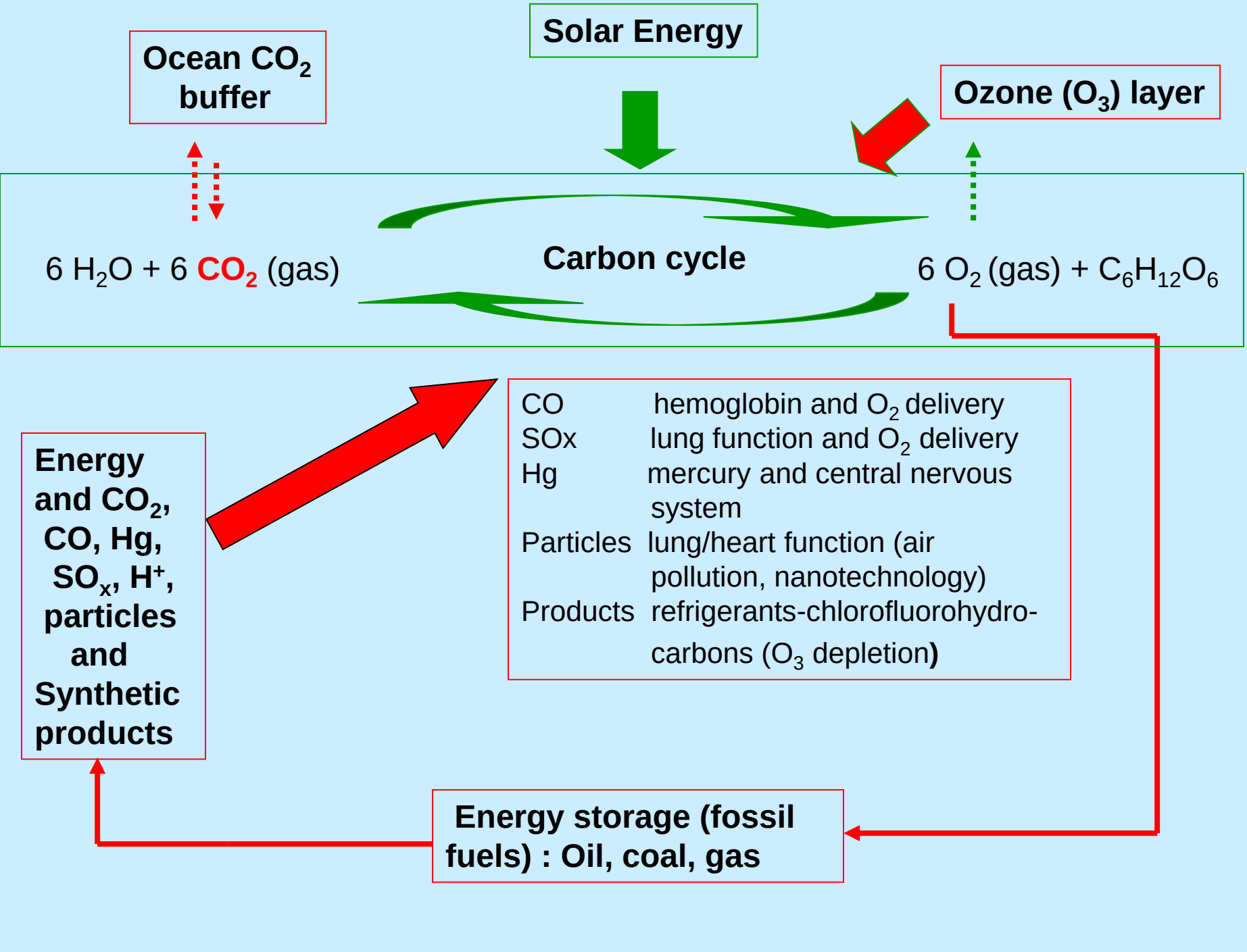
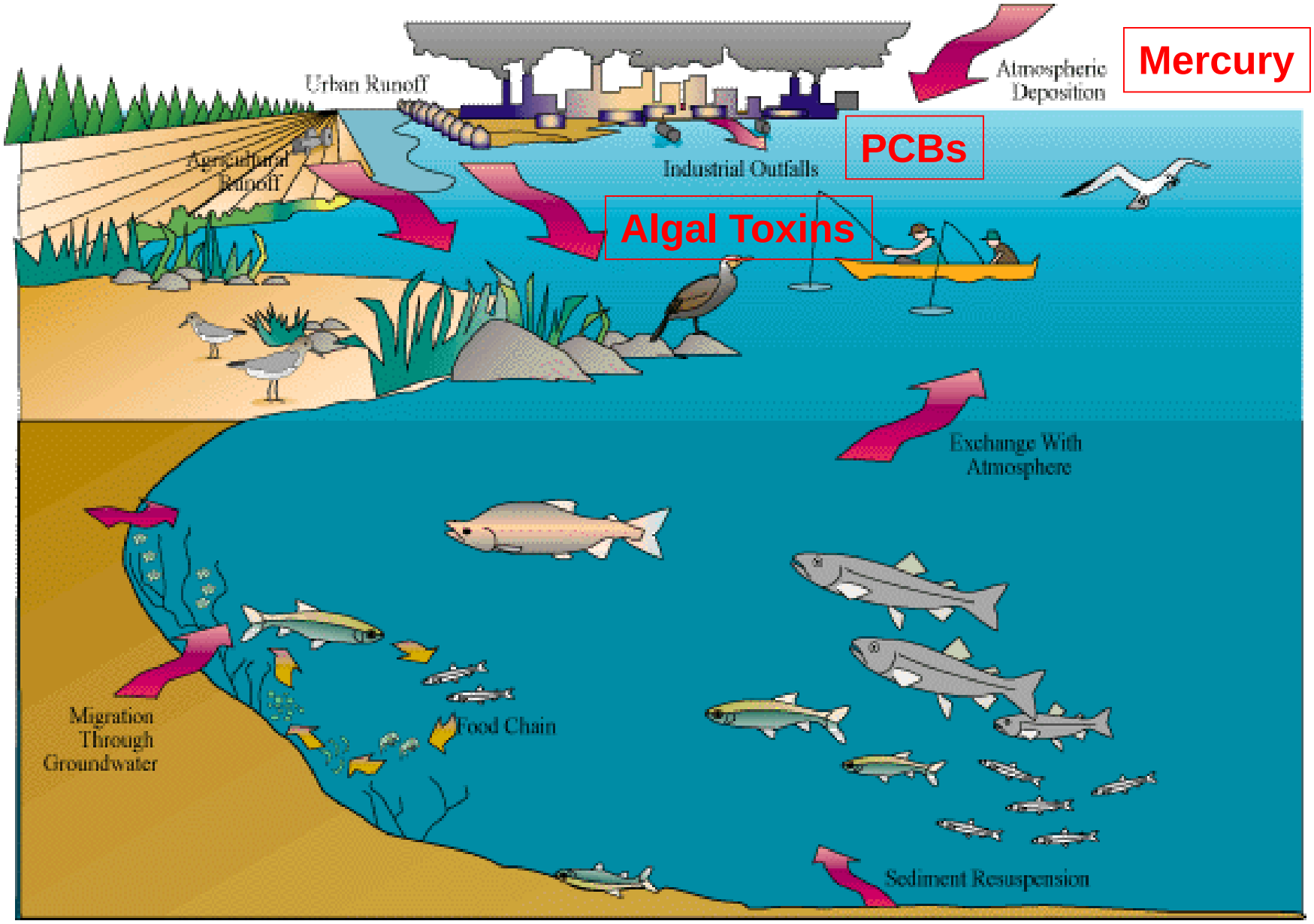


Photosynthesis and respiration at the biospheric level.
Basic environmental protections/constraints

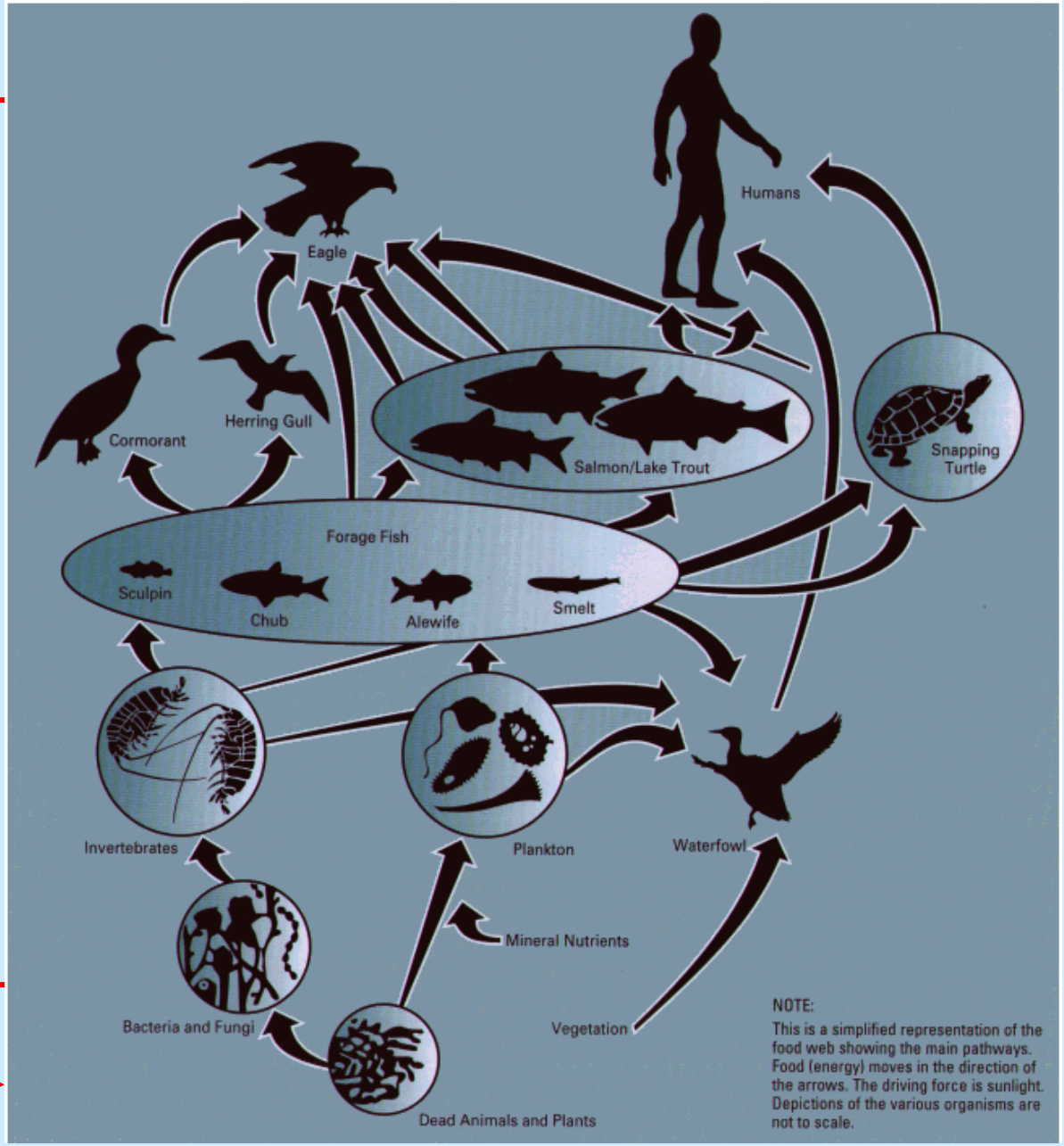

Solar Energy
Ocean CO_2 buffer
Ozone (O_3) layer
6 H_2O + 6 CO_2 (gas)
Carbon cycle
6 O_2 (gas) + $C_6H_{12}O_6$
Energy and CO_2, CO, Hg, SO_x, H^+, particles and synthetic products
Contamination
Biological energy: ATP
Combustion
Atmospheric greenhouse
Energy storage (fossil fuels) : Oil, coal, gas


Solar Energy
Ocean CO_2 buffer
Ozone (O_3) layer
6 H_2O + 6 CO_2 (gas)
Carbon cycle
6 O_2 (gas) + $C_6H_{12}O_6$
Energy and CO_2, CO, Hg, SO_x, H^+, particles and Synthetic products
CO hemoglobin and O_2 delivery
SOx lung function and O_2 delivery
Hg mercury and central nervous system
Particles lung/heart function (air pollution, nanotechnology)
Products refrigerants-chlorofluorohydro-carbons (O_3 depletion)
Energy storage (fossil fuels) : Oil, coal, gas



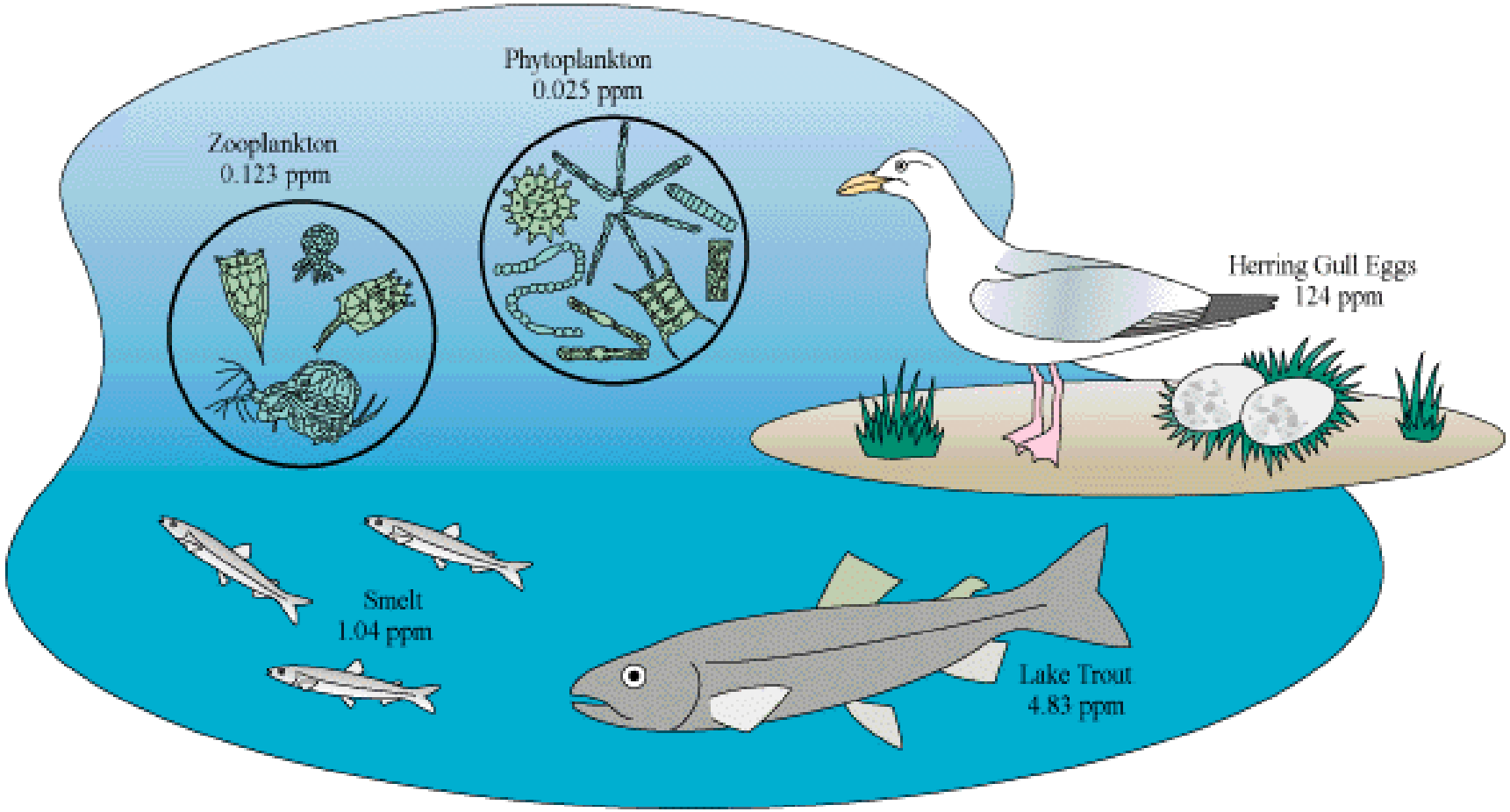
Sources and Pathways of Pollution.

http://www.epa.gov/glnpo/atlas/index.html



http://www.epa.gov/glnpo/atlas/index.html

Food Web Concentration of Organic Chemicals



Persistent Organic Chemicals *such as PCBs bioaccumulate. This diagram shows the degree of concentration in each level of the Great Lakes aquatic food chain for PCBs (in parts per million, ppm). The highest levels are reached in the eggs of fish-eating birds such as herring gulls.*

http://www.epa.gov/glnpo/atlas/index.html

Consequences of Human Dominated Ecosystems

Geologic store of carbon; global burning of fossil fuels; long and short range atmospheric distribution of mercury; concentration in aquatic foodweb because of formation of methylmercury; entrance into the food supply through eating fish.

Fish consumption-Risk communication video

Mercury Metabolism

atmosphere $Hg^0 \longrightarrow Hg^{2+}$

microorganisms protective mechanism $Hg^{2+} \longrightarrow (CH_3)_2Hg$ ↑

$(CH_3)_2Hg \longrightarrow (CH_3)Hg^+$

$(CH_3)Hg^+ \longrightarrow$ binds in fish tissues

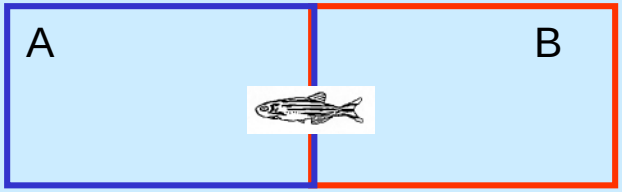
$(CH_3)Hg^+ \longrightarrow$ binds in human nerve tissue

$(CH_3)Hg^+ + \text{Protein-SH} \longrightarrow (CH_3)Hg\text{-S-Protein} + H^+$

Note: Drs.Carvan, Weber, and Petering collaborate to understand impacts of $(CH_3)Hg+$ on development: embryonic exposure causes adult deficits in visual response and learning. There is an *epigenetic* component to these outcomes.

Effects of Developmental Exposure to Chemicals on Adult Learning in Zebrafish

Exposure to chemical during first 24 h of development; testing at 8 weeks
Learning paradigm: tap middle of tank, drop food item five seconds later on side B and simultaneously observe location of fish (side A or B); wait 20 minutes and repeat the procedure, dropping the item on side A; and continue the alternating pattern.



Results

Chemical		Trials to learn task
Control		14 trials
Lead	10 µM	32
	30	never
Alcohol	10 mM	22
	30	27
Methylmercury	0.01 µM	never

Daniel Weber and
Michael Carvan

Transgenerational Impacts of Methylmercury in Zebrafish

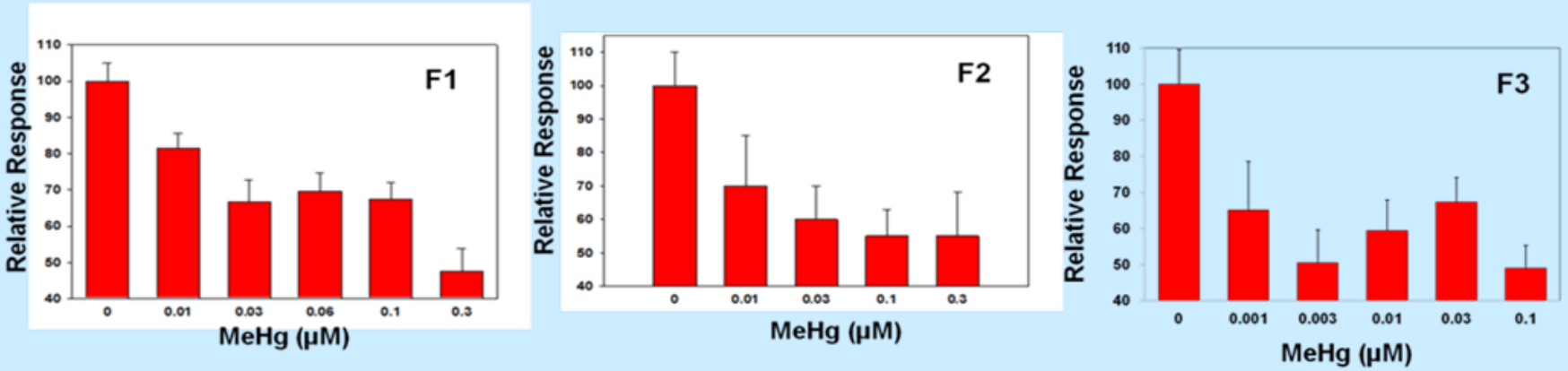
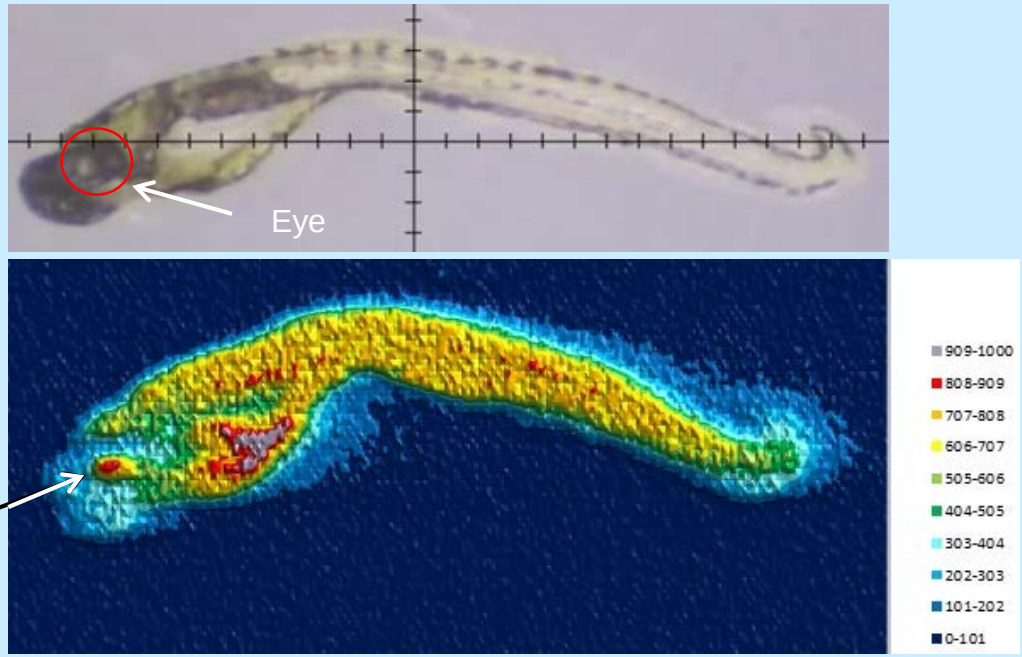


Figure 1: Effects of developmental MeHg exposure on adult visual response to a rotating black bar under low light conditions. F1 = F1 generation fish, which were directly exposed to MeHg during development. F2 = F2 generation fish (the offspring of F1 fish), which were exposed to MeHg as primordial germ cells within the F1 embryos at time of treatment. F3 = F3 generation fish (the offspring of F2), which were never exposed to MeHg. The vertical bar represents the number of responses relative to the control population. All treatment groups are significantly different than the respective controls at $P<0.05$. The number of zebrafish analyzed was ≥ 8 per treatment group.

Organism
↓
Cell
↓
Proteome
↓
Protein

LA-ICP-MS
Linking Macro- and Microscopic Measurements

Distribution of Hg in larval zebrafish 144 h post-fertilization. Embryo exposed to 0.1 uM CH_3Hg for 4-24 h post fertilization.



Embryonic CH_3Hg^+ ⟶ Inhibition of visual startle response ⟶ abnormal retinal bipolar cell electrophysiology ⟶ molecular targets?

Eye (laser capture microdissection) ⟶ proteome preparation ⟶ proteome separation ⟶ LA-ICP-MS

M. Carvan
D. Petering

Methylmercury Poisoning

Dr. Karen Wetterhahn died 10 months after spilling a drop of dimethylmercury on a 'protective' glove. She died of acute neurological (CNS) toxicity. (http://www.chm.bris.ac.uk/motm/dimethylmercury/dmmh.htm)

Exposure to 1 drop of dimethylmercury that was wiped off a glove: how many grams of mercury would remain?

2.96 g/milliliter (ml) x 0.05ml x 0.2 = 0.0296 g total exposure to dimethylmercury

(Density) (Exposure: one drop (0.05 ml), wiped off with perhaps 20% (0.2) remaining

~ 0.03 g

0.03 g dimethylmercury x 200 g mercury/230 g dimethylmercury = 0.026 g mercury

(Atomic weight of mercury/molecular weight of dimethylmercury)

Suppose this amount of mercury were diluted evenly into the entire body weight of Karen Wetterhahn. What would be the final concentration?

0.026 g/140 lbs x 2.2 lbs/kilogram = 0.00041 g mercury/kg body weight ($4.1 \times 10G^4$)
(mercury weight (conversion factor) (0.41 mg/kg body weight)
divided by body weight)

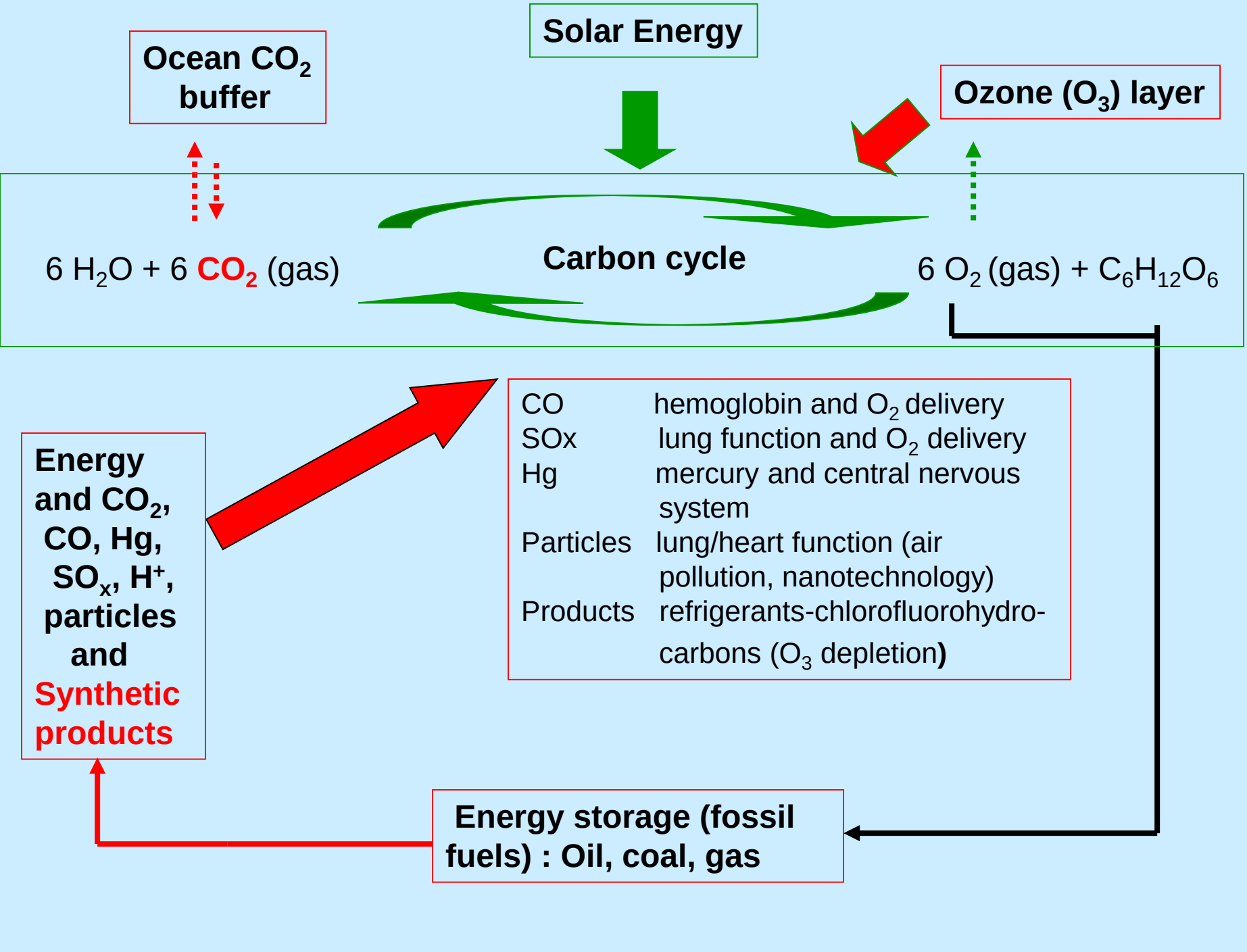
0.00041 g mercury/kg body weight x 1 kg/1000 g = 0.00000041 g mercury/g body weight

(conversion factor)

0.00000041 g mercury/g body weight x 1,000,000 micrograms/g = 0.41 microgram
(conversion factor) mercury/g body weight
0.41 ppm (parts per million)

This is 8 times the maximum permissible limit in blood. In fact, Dr. Wetterhahn's actual blood level was 80 times the maximum level, showing that the toxic mercury had concentrated in some parts of the body, probably including the central nervous system of the brain.

Dr. Wetterhahn's gloves did not protect her against dimethylmercury.


Solar Energy
Ocean CO_2 buffer
Ozone (O_3) layer
6 H_2O + 6 CO_2 (gas)
Carbon cycle
6 O_2 (gas) + $C_6H_{12}O_6$
Energy and CO_2, CO, Hg, SO_x, H^+, particles and Synthetic products
CO hemoglobin and O_2 delivery
SOx lung function and O_2 delivery
Hg mercury and central nervous system
Particles lung/heart function (air pollution, nanotechnology)
Products refrigerants-chlorofluorohydro-carbons (O_3 depletion)
Energy storage (fossil fuels) : Oil, coal, gas

Chemical/Synthetic Society

Urban
Rural
Occupational

Food	industry-synthetic food, additives, preservatives, antibiotics, pesticides, herbicides, fertilizers
Clothing	synthetics, petrochemicals
Shelter	plastics, synthetic materials, paint, treated wood
Transportation	petrochemicals, batteries
Lifestyle	cosmetics, …

Transition: natural to synthetic

TRI-POWER® SELECTIVE

HERBICIDE

FOR SELECTIVE BROADLEAF WEED CONTROL IN ORNAMENTAL LAWNS AND TURF GRASSES

ALSO FOR WOODY PLANTS, ROADSIDES, AND SIMILAR NON-CROP AREAS.

CONTROLS: Dandelion, Chickweed, Black medic, Knotweed, Plantain, Oxalis, Clover, Cocklebur, Thistle and many other species of broadleaf weeds; some of which are listed on this label.

CONTAINS MCPA, MECOPROP-p AND DICAMBA

GET THE OPTICAL ADVANTAGE™

ACTIVE INGREDIENTS:	
Dimethylamine Salt of 2-Methyl-4-Chlorophenoxyacetic Acid*	40.42%
Dimethylamine Salt of (+)-R-2-(2-Methyl-4-Chlorophenoxy)propionic Acid**	7.99%
Dimethylamine Salt of Dicamba (3,6-Dichloro-o-Anisic Acid)***	3.97%
INERT INGREDIENTS:	47.62%
TOTAL	100.00%

By Isomer Specific AOAC Method, Equivalent to:

*2-Methyl-4-Chlorophenoxyacetic Acid	33.00%, 3.1 lbs./gal.
**(+)-R-2-(2-Methyl-4-Chlorophenoxy)propionic Acid	6.60%, 0.6 lbs./gal.
***3,6-Dichloro-o-Anisic Acid	3.30%, 0.3 lbs./gal.

For Control of Woody Plants: Apply to both stems and foliage any time from the time foliage is completely matured until the time plants start to go dormant. All leaves, stems and suckers must be completely wet to the ground line for effective control. Regrowth may be anticipated on the more resistant species. Add ⅔ gallons of Tri-Power to 100 gallons of water applying 200 to 600 gallons of spray mixture per 43,500 square feet depending upon the height and thickness of the brush. Mix thoroughly before spraying.

Mixture

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Google: Extoxnet
reagent

Toxicity (LD50)

	Small Animals	Actual pesticide weight for 100 g animal		
Aldicarb	1-10 mg/kg	0.1-1 mg	0.0001-0.001 g	0.0000035 - 0.000035 oz
MCPA	700 mg/kg	70 mg	0.07 g	0.0024 oz
Mecoprop	1000 mg/kg	100 mg	0.1 g	0.0035 oz
Dicamba	2000 mg/kg	200 mg	0.2 g	0.007 oz
Roundup	5000 mg/kg	500 mg	0.5 g	0.018 oz

	Actual weight for 30 kg human	Actual weight for a 10 g bird
Aldicarb	30-300 mg	0.01-0.1 mg
MCPA	21,000 mg (21 g)	7 mg
Mecoprop	30,000 mg (30 g)	10 mg
Dicamba	60,000 mg (60 g)	20 mg
Roundup	150,000 mg (150 g ~ 0.3 lbs.)	50 mg

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2/3 gal Tri-power/ 100 gal water

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600 gal/43,000 sq ft

2/3 gal Tri-power/ 100 gal water x 600 gal/43,000 sq ft = 4 gal/ 43,000 sq.ft.

Tripower

MCPA (40%)
Mecoprop (8%)
Dicamba (4%)

Recommended Application: 1 gallon/10,000 sq. ft.

1 gal ~ 4 liters

If the density of the solution is about 1g/ml, then 1 gallon weighs about 4000 g

So, 4,000 g of **Tripower** will be distributed over 10,000 sq ft or 0.4 g/1 sq. ft.
Therefore, 0.4 g or 400 mg will contain

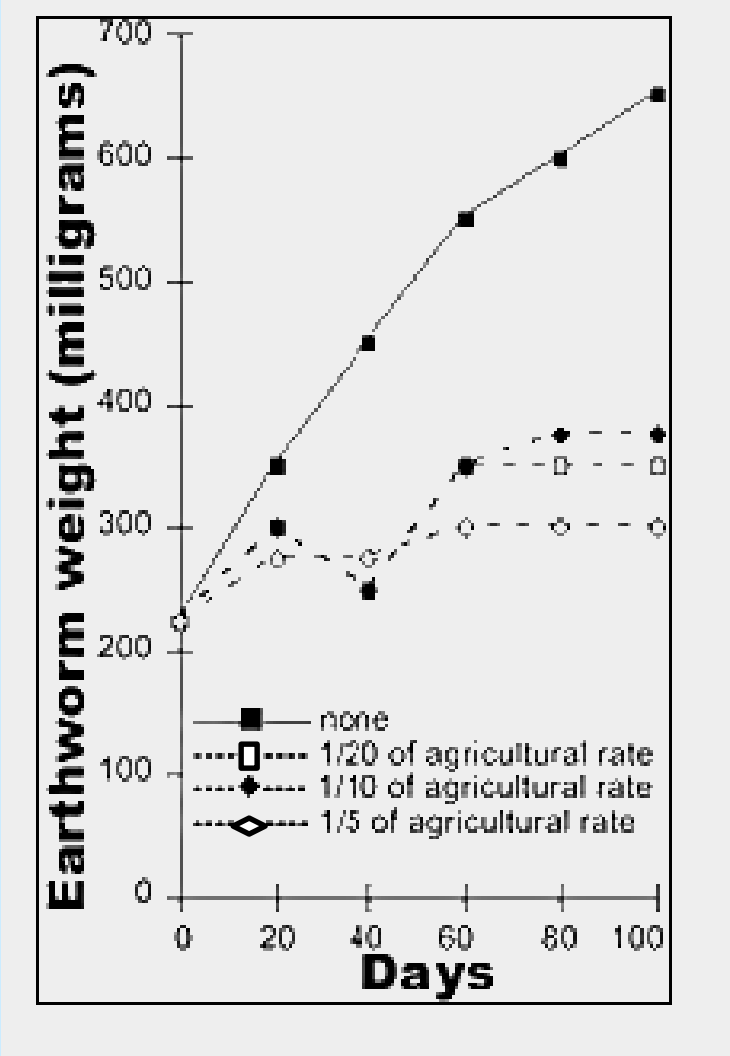
160 mg MCPA (400 x 0.4 or 40%)
32 mg Mecoprop (400 x 0.08 or 8%)
16 mg Dicamba (400 x 0.04 or 4%)

10 g bird
23 X LD-50
3.2 X
0.8 X

What do these calculations mean for a 10 g bird?
How many sq. ft. contain the LD50 amount of each pesticide? Of the combination?

	LD50	**Tri-power application area containing LD50**	**Degradation half-time**
MCPA	7 mg	0.044 (7/160) sq. ft. (160 mg/1 sq. ft = 7 mg/ x)	14-28 days
Mecoprop	10 mg	0.33 (10/32) sq. ft.	15 days
Dicamba	20 mg	1.2 (20/16) sq. ft.	7-28 days

Glyophosate (Roundup) Factsheet: Caroline Cox / Journal of Pesticide Reform v.108, n.3 Fall98 rev.Oct00



Springer, J.A. and R.A.J. Gray. 1992. Effect of repeated low doses of biocides on the earthworm Aporrectodea caliginosa in laboratory culture. Soil Biol. *Biochem.* 24(12): 1739-1744.

Key Concepts in Environmental Health

Multiple Exposures-Mixtures

Exposure: functions of multiple materials/chemicals and time

Lung Damage Lingers after 9/11

Aldrich et al, N. England J. Medicine, 362, 1263 (2010)

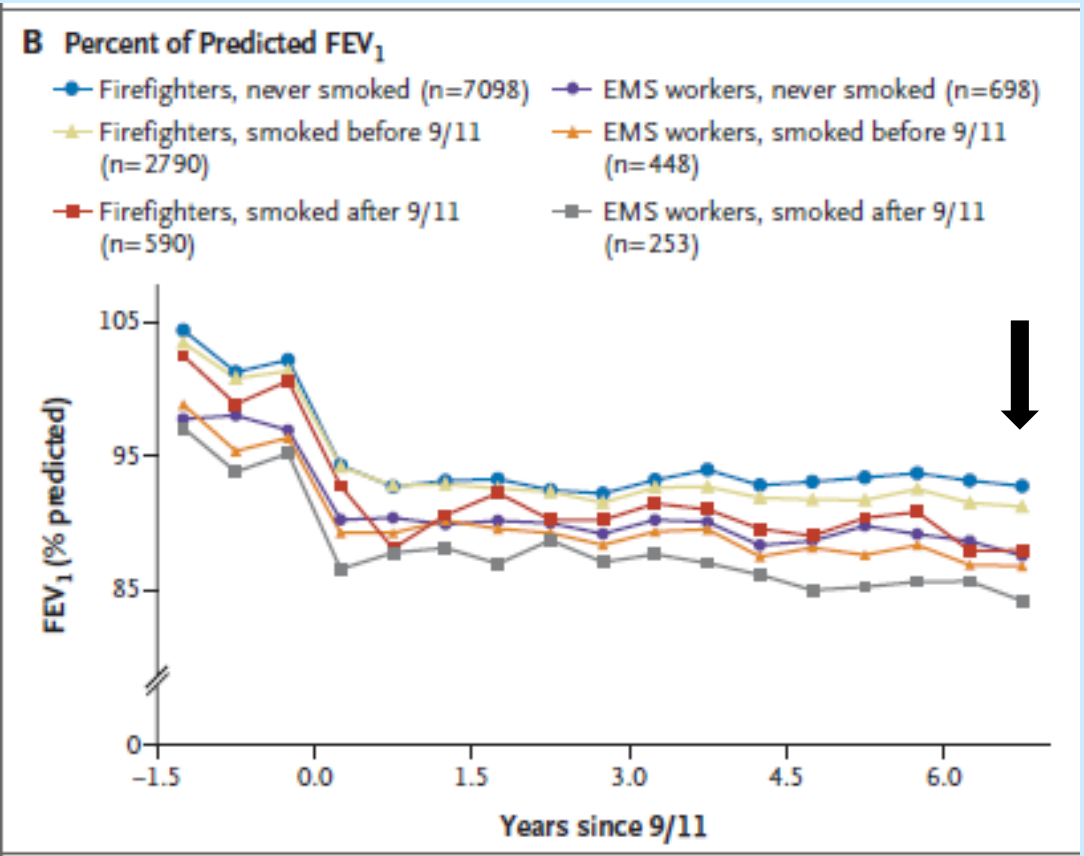


Figure 2. Lung Function in Firefighters and Emergency-Medical-Services (EMS) Workers, According to Smoking Status.

Panel A shows mean forced expiratory volume in 1 second (FEV_1) values (with adjustment for race, sex, height, and age on September 11, 2001 [9/11]) for Fire Department of New York City workers at the World Trade

After 7 years (2008), markers of lung function had not recovered in first responders to 9/11 building collapses.

Exposure mixture: glass fibers, high pH concrete dust, gases, many other constituents (pulverized building materials), cigarette smoke!

Environmental exposures occur in mixtures not as single chemicals as in laboratory experiments

Key Concepts in Environmental Health

Vulnerable populations: children

Windows of Vulnerability

- During development (conception – adolescence)
- During illness or injury
- During aging

Development

Fetal: organogenesis
fetal basis of adult disease (epigenetic impact)
obesity, diabetes, heart disease, respiratory function, etc.

Early: first encounters with environment: infants breathe air closer to the ground, they breathe faster than adults and take in and metabolize more oxygen per weight. They eat more food but with less variety. They put their hands on the ground and in their mouths. ETC.

Later: cognitive development continues for many years.

Milwaukee City Health Statistics

Children

Lead poisoning — 6.6% (>10 g/dL)
http://www.ci.mil.wi.us/LeadPoisoningFacts

Asthma — 30,000 (Milwaukee county, 2007)
http://www.chw.org/display/PPF/DocID/36962/Nav/1/router.asp

14% primary school children (2002)
27% 1-3 year olds (2002)
Asthma Surveillance in Urban Public Schools and WIC clinics, Medical College of Wisconsin

Overweight and Obesity — 40% and 23%
Citywide Nutrition and Physical Activity for Urban Children and Families project: United Neighborhood Centers of Milwaukee (Milwaukee Journal-Sentinel, July 20, 2008, 2B)

Low birth weight — 10%
http://dhs.wisconsin.gov/localdata/infantspgwomn/START.HTM

Environmental Lead, Exposure, and Health Effects

Automobile exhaust – phase out 1972-1986

Pre-1980s: blood lead concentrations commonly > 40 □g/100 ml – frank neurological poisoning with convulsions; anemia

Paint: House dust and soil contamination - Phase out 1971-1977

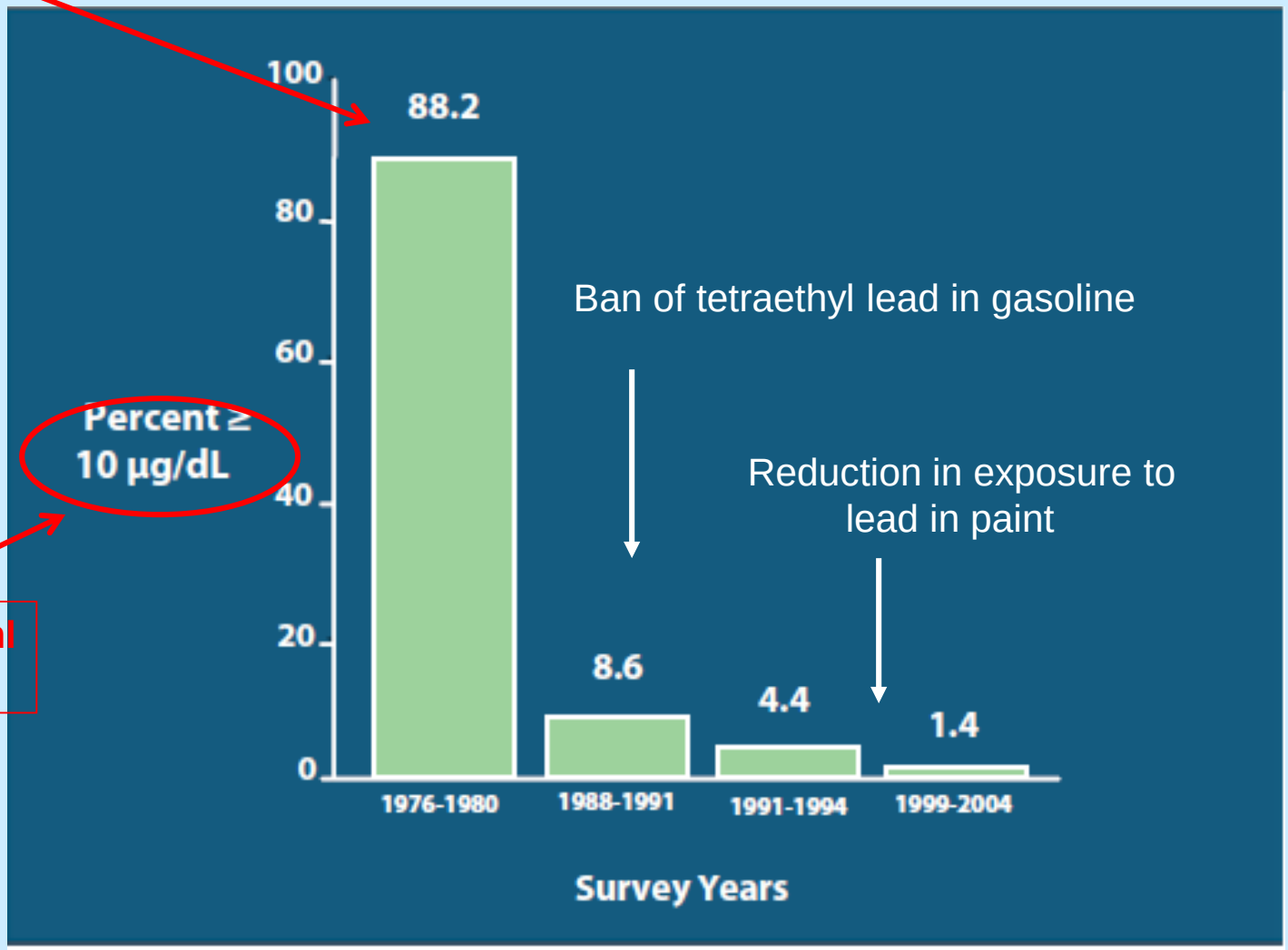
Present: blood lead for treatment: ≥ 5 □g/100 ml (0.05 ppm)

In Milwaukee, - 6.6% exceeded 10 □g/100 ml, mostly Latino and African American children

http://billmoyers.com/episode/full-show-the-toxic-politics-of-science/

Chemical Hygiene

40 µg/100 ml



5 µg/100 ml
0.05 ppm

Figure 1. Percentage of children 1-5 years old in the U.S. population with elevated blood lead levels (≥ 10 µg/dL).[1]

[1] Jones RL, Homa DM, Meyer PA, Brody DJ, Caldwell KL, Pirkle JL, Brown MJ. Trends in blood lead levels and blood lead testing among U.S. children aged 1 to 5 years, 1988–2004. Pediatrics 2009;123(3):e376-e385.

Environmental Lead, Exposure, and Health Effects

History

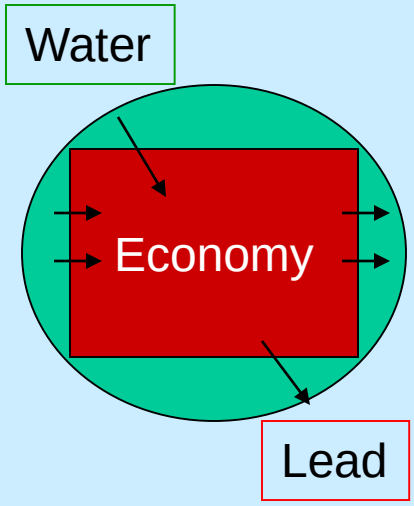
Contamination routes: Auto exhaust house paint (50% lead)

1970s downtown street dust: ~0.1% lead

Current home soil Pb: ~0.03 % lead

Hair sampling on southwest side: elevated lead downwind from battery smelter

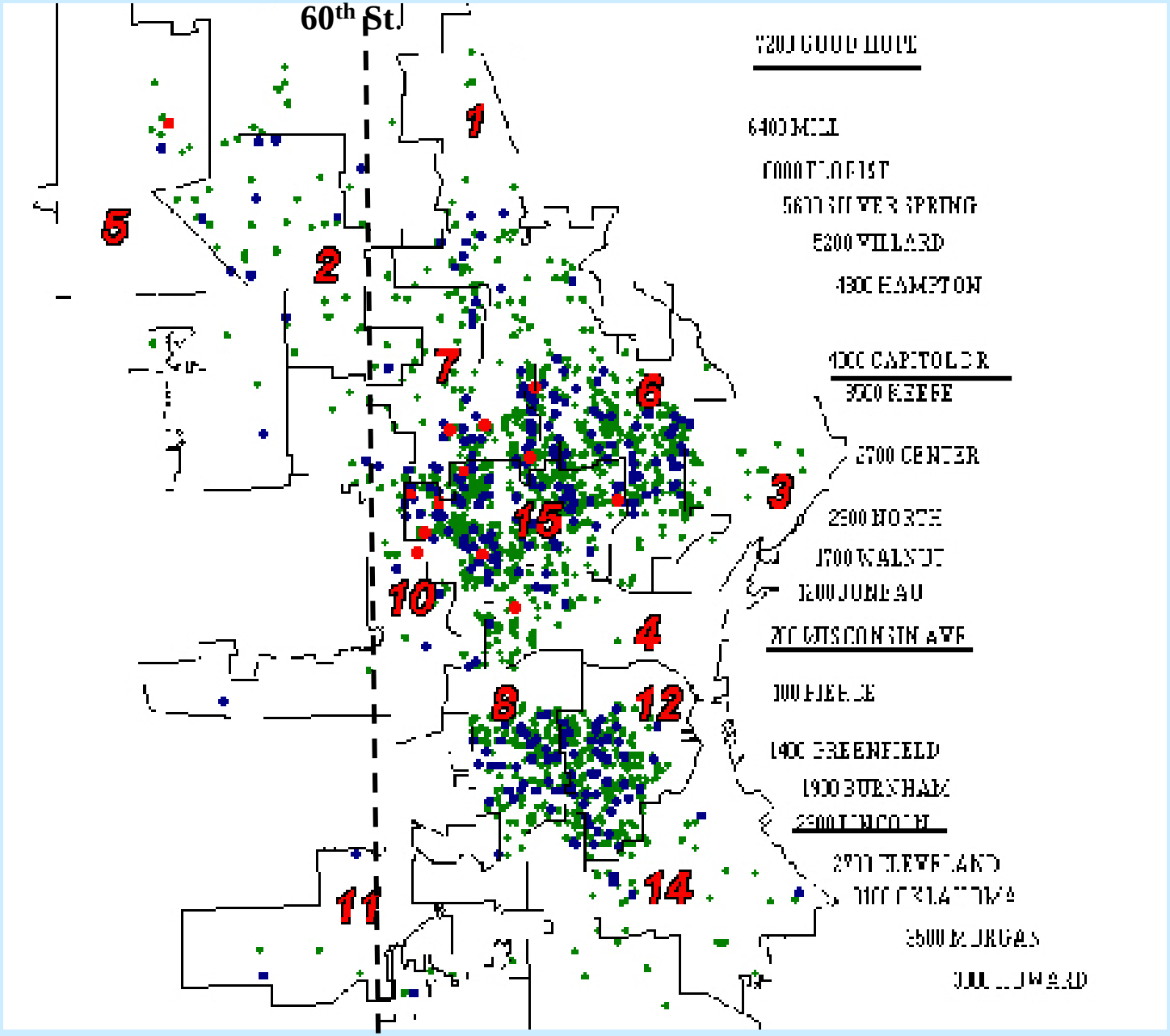
Milwaukee Metropolitan Sewerage District handling of environmental lead



	Jones Island Influent	Effluent	Milorganite
1975	400 lbs/day	130	690 mg/kg
1980	150	49	390
1990	67	58	200
2000	18	2	68
2007	12	3	52

City of Milwaukee Lead Prevention Program - 2005

- 14 children >44 µg/dL
- 392 children 20-44 µg/dL
- 1692 children 10-19 µg/dL



Environmental Lead, Exposure, and Health Effects

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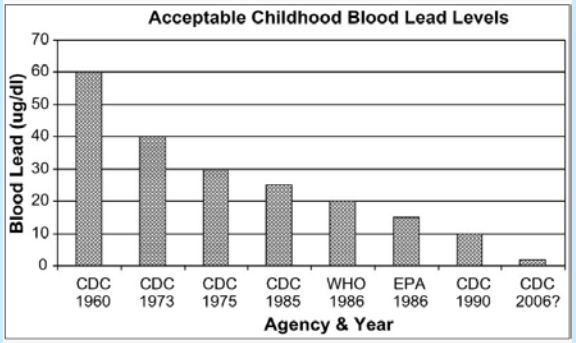
Paint: House dust and soil contamination - Phase out 1971-1977

Soil contamination: routinely 400 ppm (0.04%)

Present: maximal permissible blood lead limit - 5 □g/100 ml

In Milwaukee, - 6.6% exceed this level, mostly Latino and African American children
Above this level, more subtle neurological effects – cognitive deficits (IQ reduction), hyperactivity, …

Studies show effects below 10 □g/100 ml !

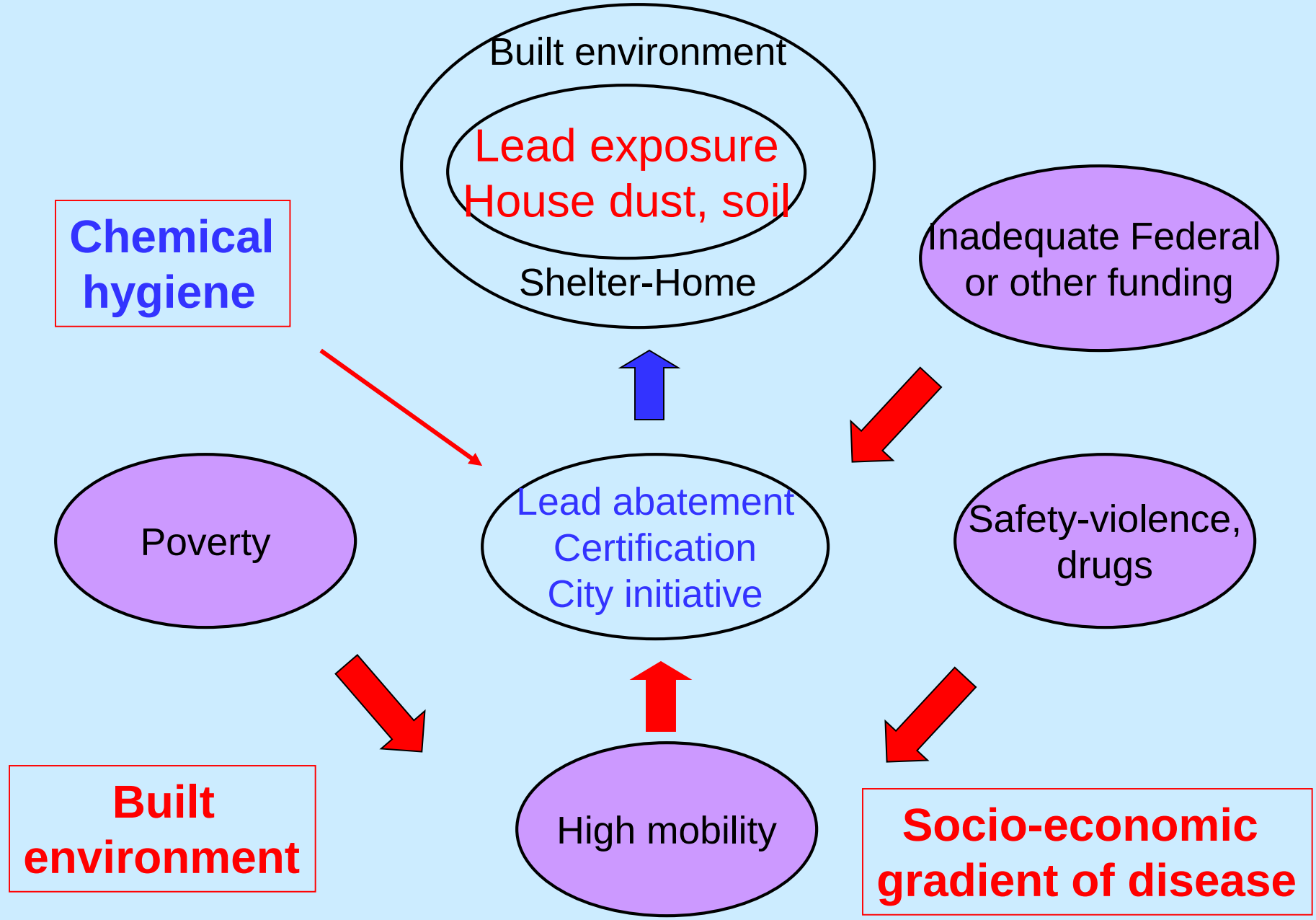


S.G. Gilbert and B. Weiss, A rationale for lowering the the blood lead action level from 10 to 2 microg/dL,Neurotoxicology, 27, 693-701 (2006)

Key Concepts in Environmental Health

Role of the Built Environment

What Can Be Done to Limit Exposure to Lead ?



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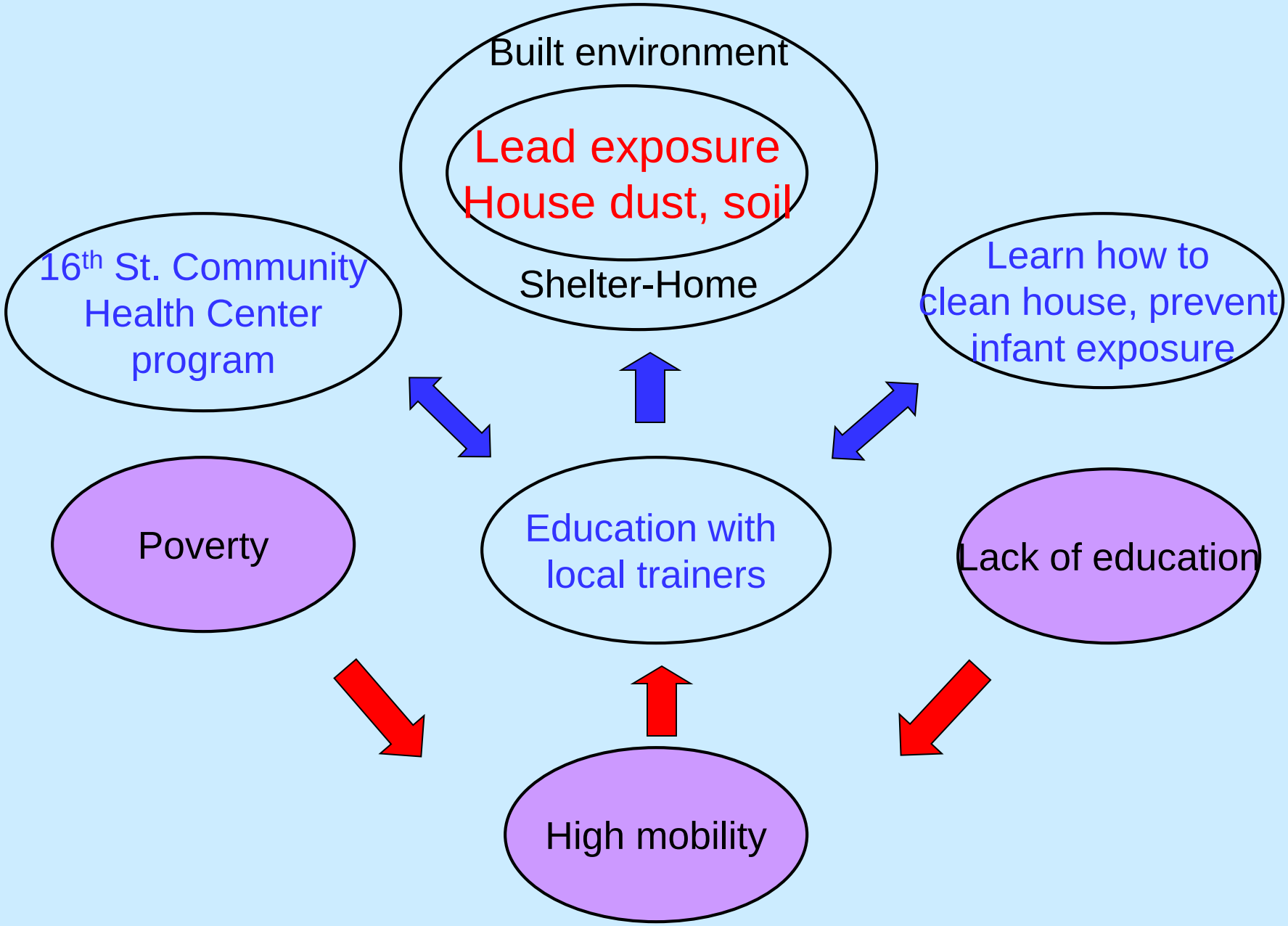

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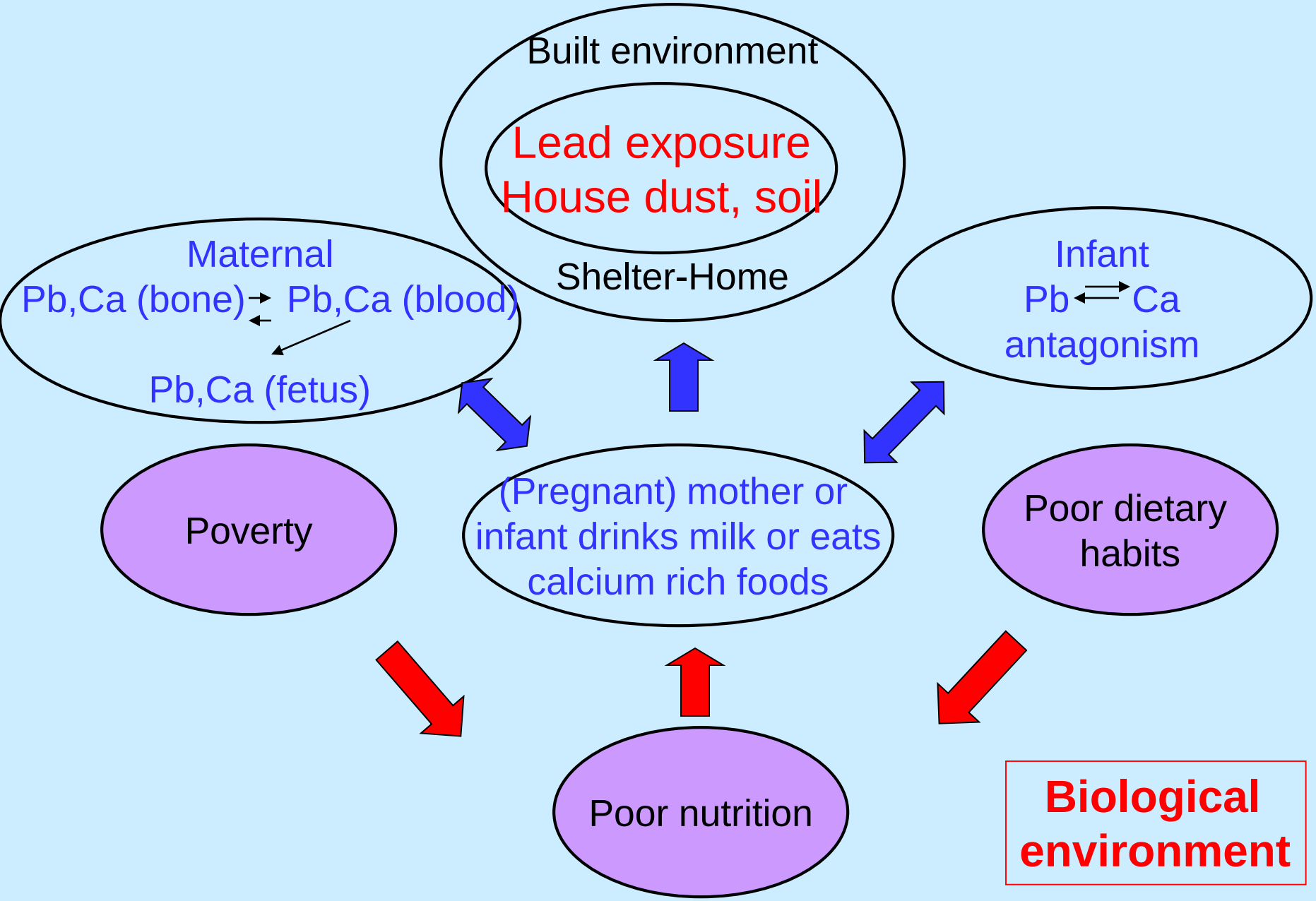
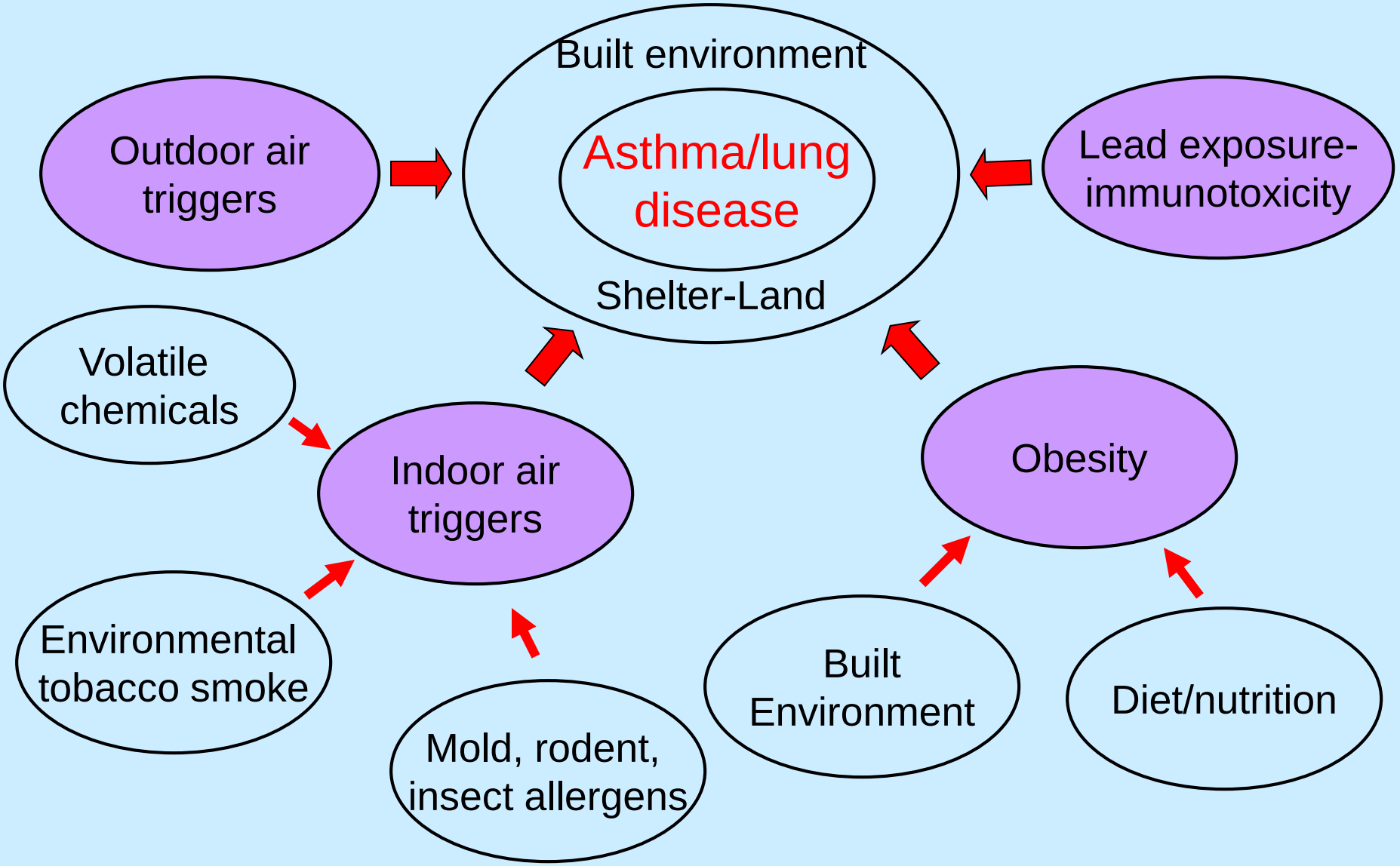


Key Concepts in Environmental Health

Multiple confounding factors

Major Health Problem of the Built Environment

Unexpected connections throughout the built environment



Key Concepts in Environmental Health

Causal relationships

How Shall We Understand and Address These Environmental Health Issues?

Understanding as a basis for action

- **Causality**

When can scientists decide that A causes B?

- Single cause (infectious agent)
- Close temporal relationship between exposure and effect
- Obvious, acute effect
- Duplicate effects in the laboratory (single variable experiment)

When is it difficult to link A with B?

- Multiple causative factors that contribute in different ways (A (susceptibility factor); B (environmental-direct action factor, permissive factor)
- Slowly developing (chronic) effect
- Difficulties in linking population (multi-factor) and laboratory (controlled, single factor) studies

Understanding as a basis for action

- **STEM as major tool**

- **Vulnerable populations**

  fetus, children, elderly, genetically pre-disposed individuals and groups

- **Precautionary Principle** – the Ecology Principle: everything is connected to everything else

  Less than secure population or laboratory studies implicate **A** as a cause of **B**. This is a common situation in environmental health research.

  Policy stance in the face of uncertainty: "When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

  Scientists' statement: 1998 Wingspread Conference, Racine, WI

Environment-environmental Health Continuum

Our health is related to the condition/health of the environment

Human genetic constitution/genome has not changed significantly in the last 10,000 years, but our environment has radically changed.

Most of our increase in life span is due to better “hygiene” or public health - clean air and water, stable sources of nutritious food, adequate shelter, good biological and chemical hygiene, etc. In a word, these are facets of public health.

Public health, by definition, focuses on populations, communities, and environments. Health improvements are founded on (re)establishing healthy interactions/connections between these components.