Berryology 101

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BHBS 2011

Outline

1. Introduction:
   - Natural Products
   - Plant Foods/Berries and Human Disease: Obesity, Cancer, Diabetes
2. Berry Research :
   - Terminologies
   - Challenges and Issues
3. Discussion

Plant Medicines

- Plant medicines have been used by ancient cultures for centuries e.g. Traditional Chinese Medicine, Ayurveda, etc.
- The WHO estimates 80% of developing countries currently use plants as basis of medicinal systems
- Used as foods, extracts, teas, tinctures, soups, herbs, spices, etc.

Natural Products from Plants

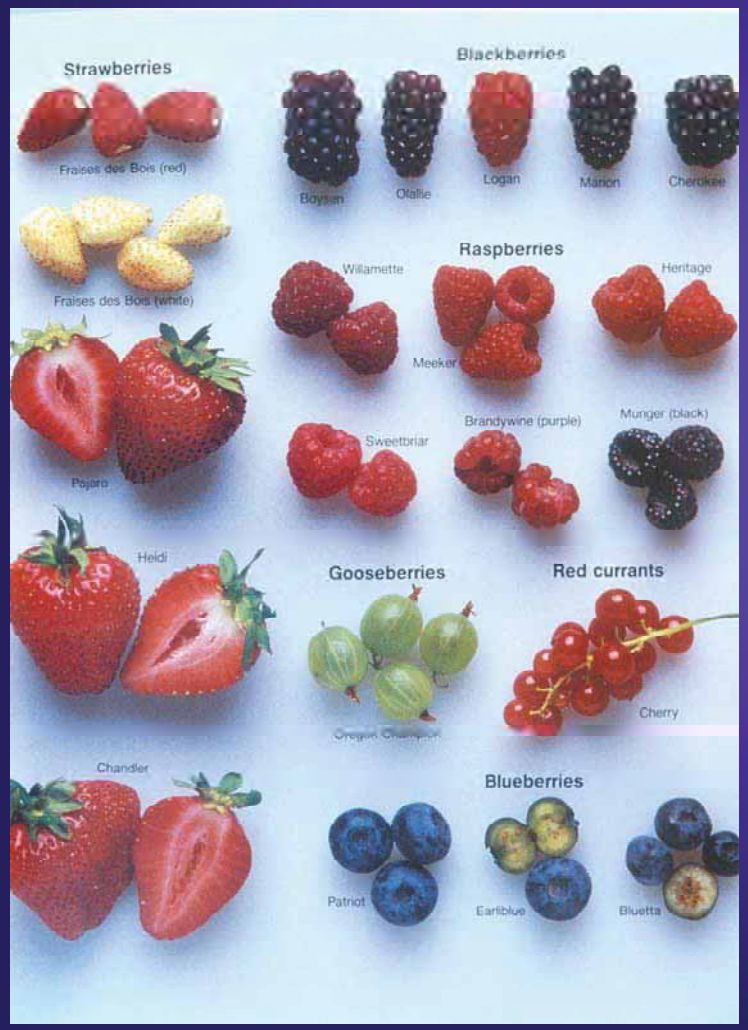
Colors in Plants

Protects from solar irradiation & oxidative damage.

Dietary Phytochemicals (Phyto = Plant)

- Epidemiological data suggest that phytochemical-rich diet reduces risk of human diseases e.g. certain cancers, heart disease, neurodegenerative diseases, etc.

Berries : ‘Super-Fruit’; rich in phenolics



Phenolics

Flavonoids

- Anthocyanins
- Flavonols
- Flavanols

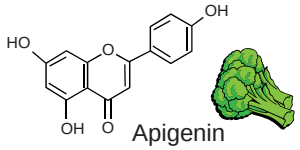
Simple Phenolics

Tannins:
Hydrolyzable
Condensed

Examples of Dietary Polyphenols

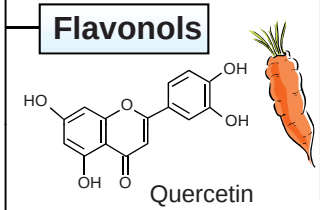
Flavonoids

Flavones



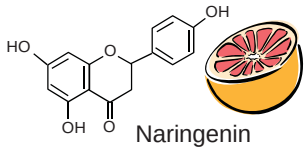
Apigenin

Flavonols



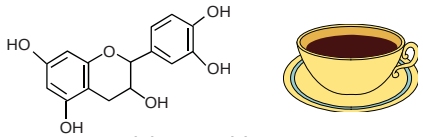
Quercetin

Flavanones



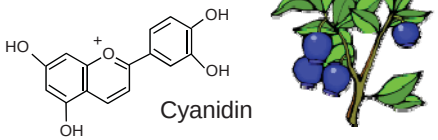
Naringenin

Flavanols (Catechins)



(+)-Catechin

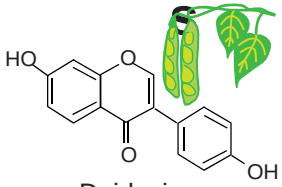
Anthocyanins



Cyanidin

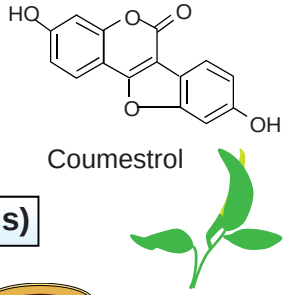
Isoflavonoid

Isoflavone



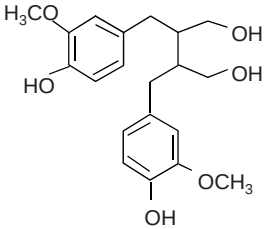
Daidzein

Coumestans



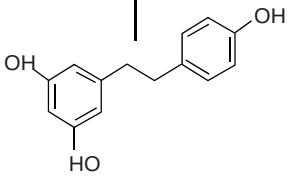
Coumestrol

Lignans



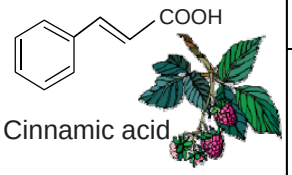
Secoisolariciresinol

Stilbenes

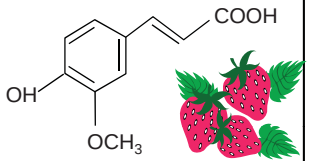


Resveratrol

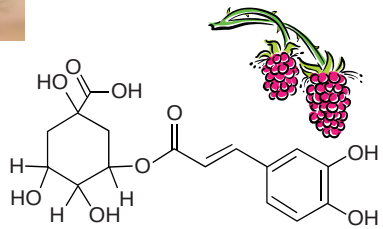
Phenolic acids



Cinnamic acid



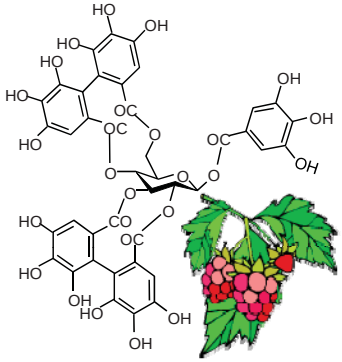
Ferulic acid



Chlorogenic acid

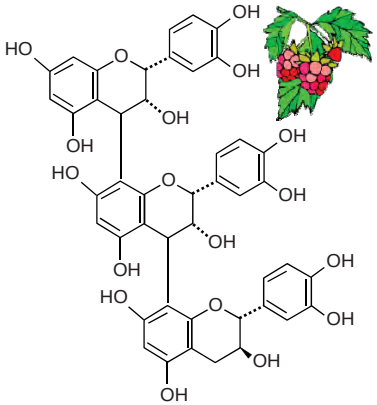
Phenolic polymers

Ellagitannins



Casuariin

Proanthocyanidin



Procyanidin trimer
(flavanol)

Importance of Plant-Based Diets:
Ancient Man vs. Modern Man

- In tropical Africa, man wandered over large areas and ate over 800 varieties of foods, providing over 25,000 different phytochemicals

- Fewer than 20% of all Americans eat five or more servings of fruits and vegetables a day, as recommended by the National Cancer Institute (NCI)

Similar DNA, different diets!

Diets Then and Now

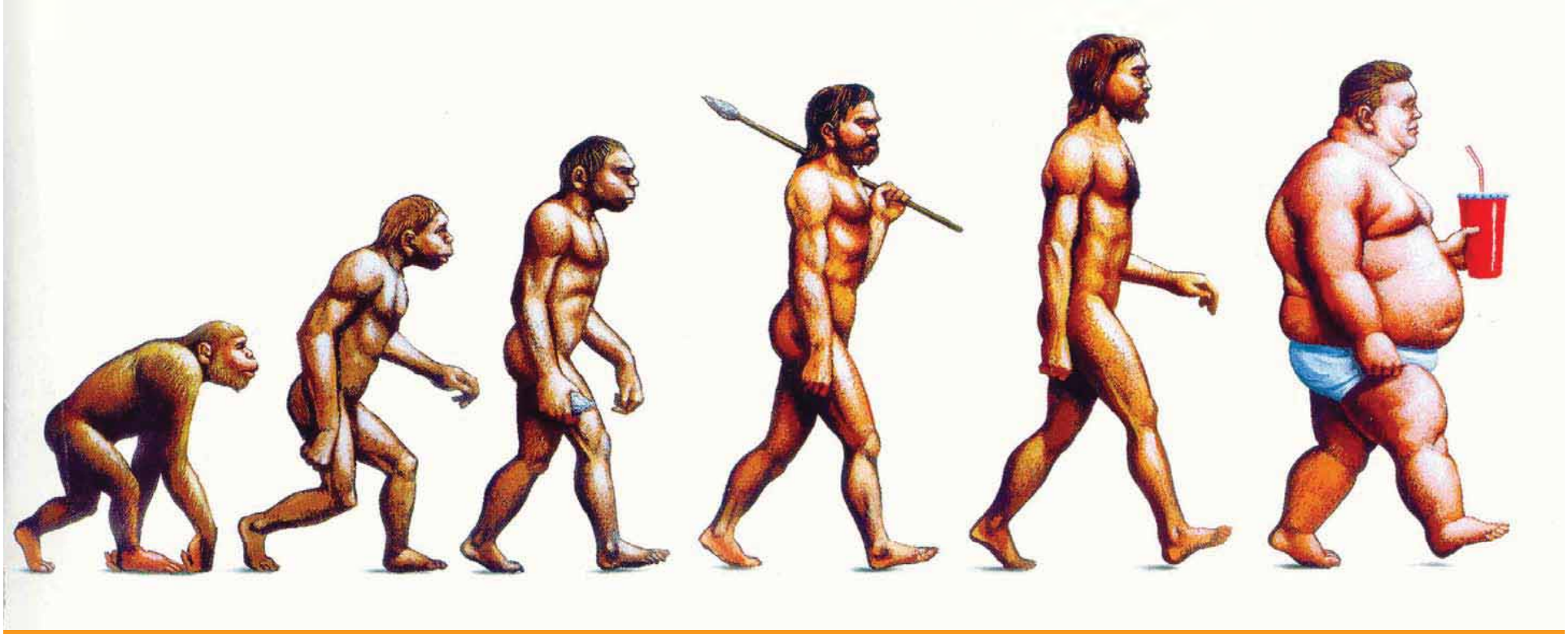
50,000 Years Ago

- Fruits, nuts, seeds, roots, tubers, flowers, leaves, stalks, beans
- (Hunter/Gatherers)

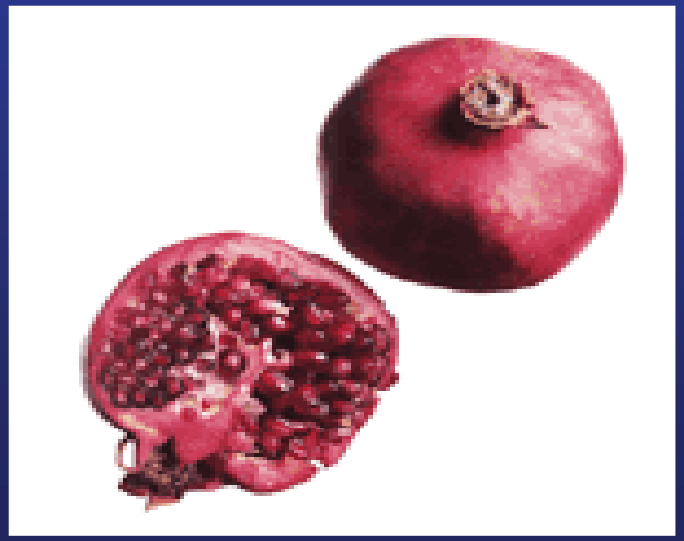
Today

- Processed foods: refined pasta, cereals white rice & flour
- Added fat and sugar
- Tobacco and alcohol
- (Sedentary Lifestyle)

Divergence from Plant- Based Diet

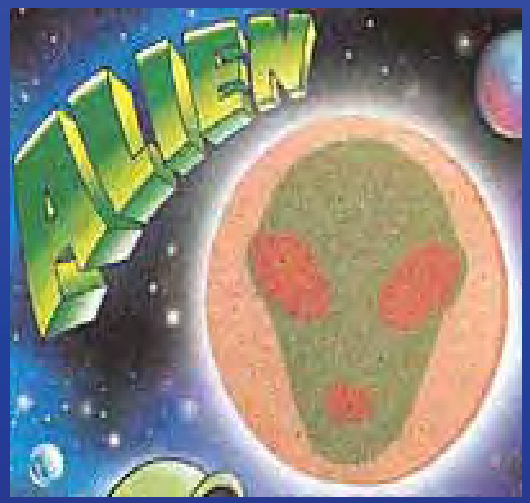


Instead of these colors…..



We eat these colors...

And these colors…



And Sedentary Lifestyles……

"Childhood obesity is at epidemic levels in the United States."

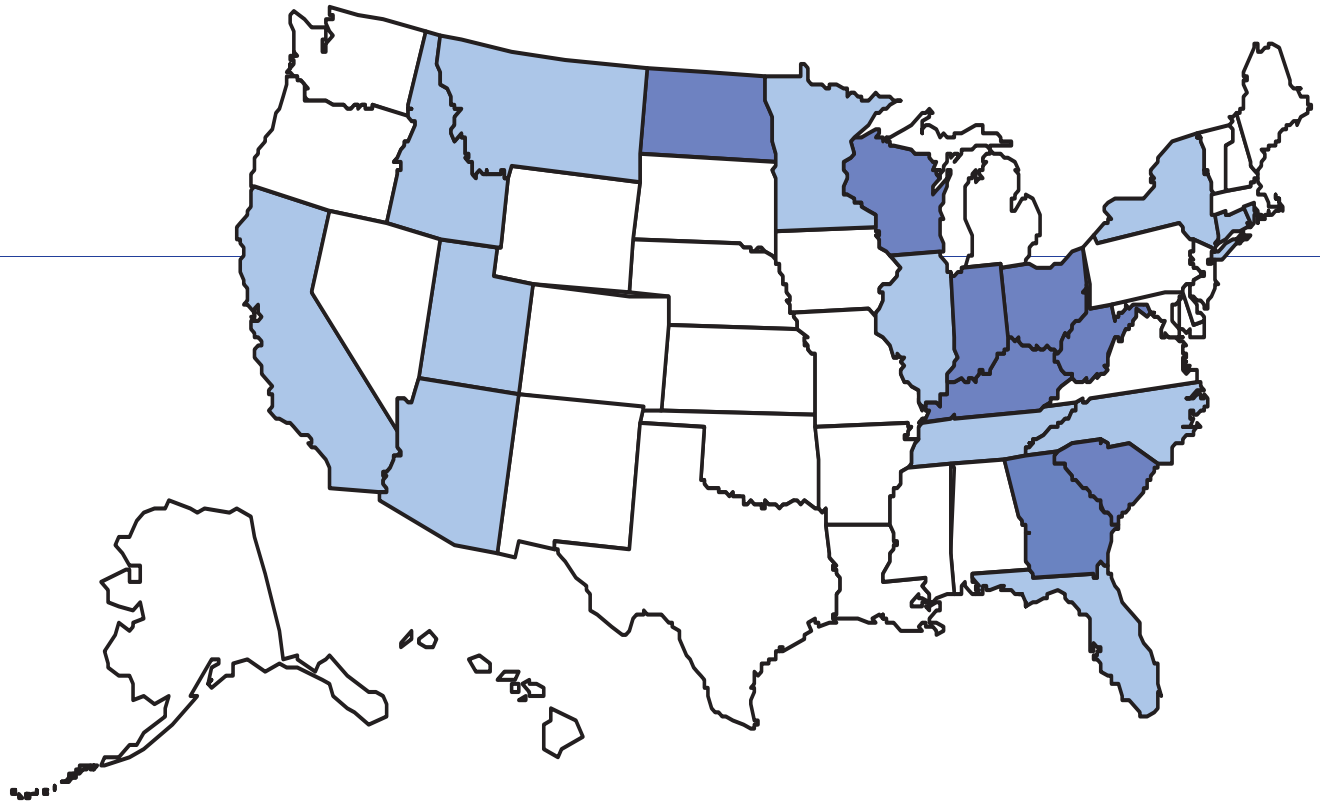
- David Satcher

US Surgeon General

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



No Data | <10% | 10%-14% | 15-19% | ≥ 20%

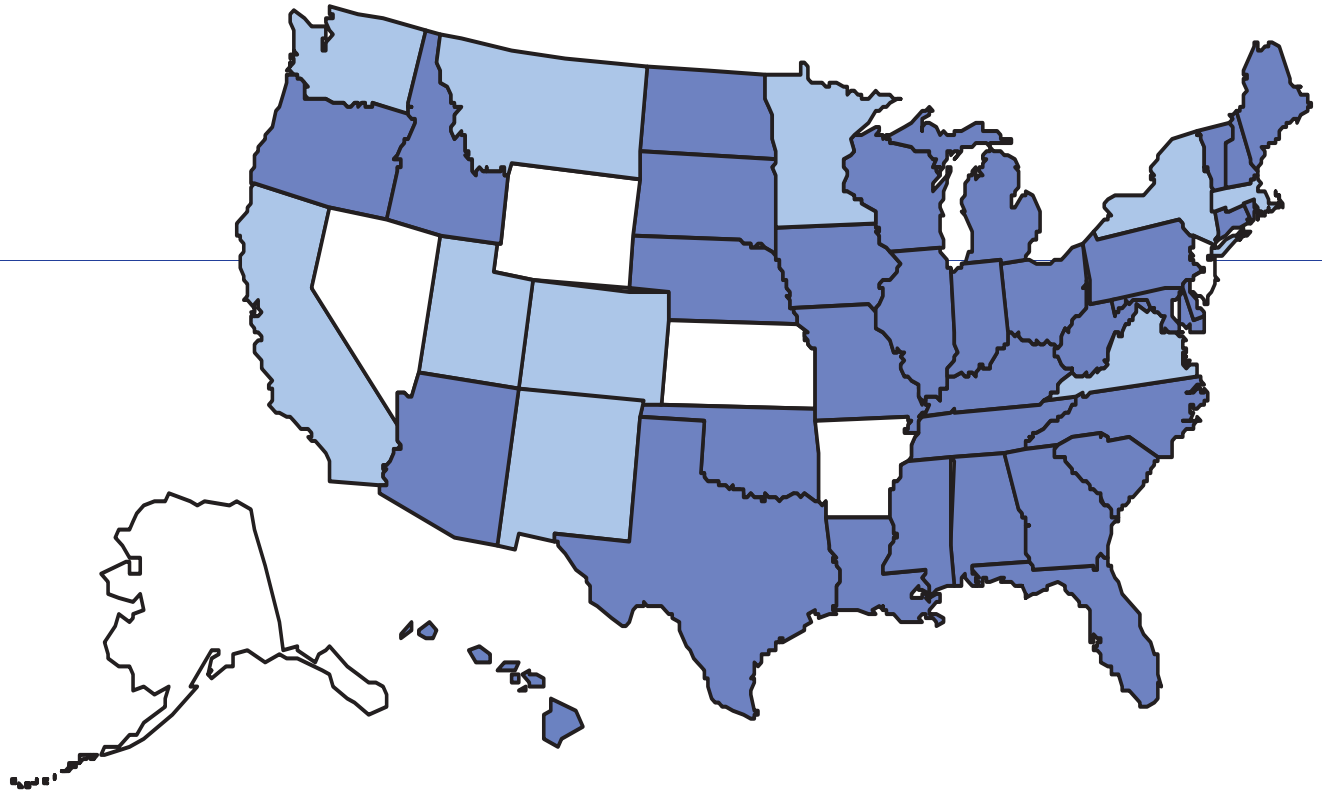
Source: Mokdad AH.

CDC
Centers for Disease Control and Prevention

Obesity Trends* Among U.S. Adults

BRFSS, 1990

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



No Data | <10% | 10%-14% | 15-19% | ≥ 20%

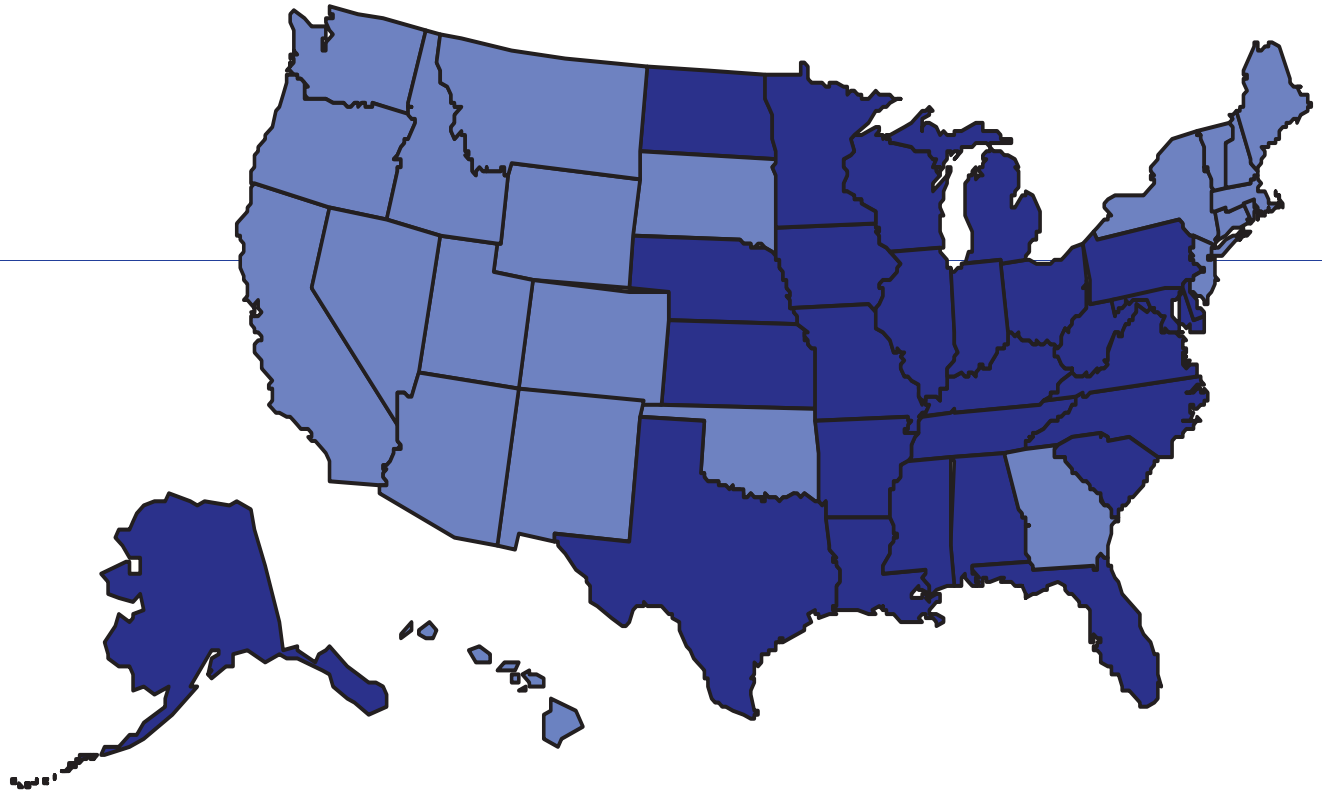
Source: Mokdad AH.

CDC
Centers for Disease Control and Prevention

Obesity Trends* Among U.S. Adults

BRFSS, 1995

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



No Data | <10% | 10%-14% | 15-19% | ≥ 20%

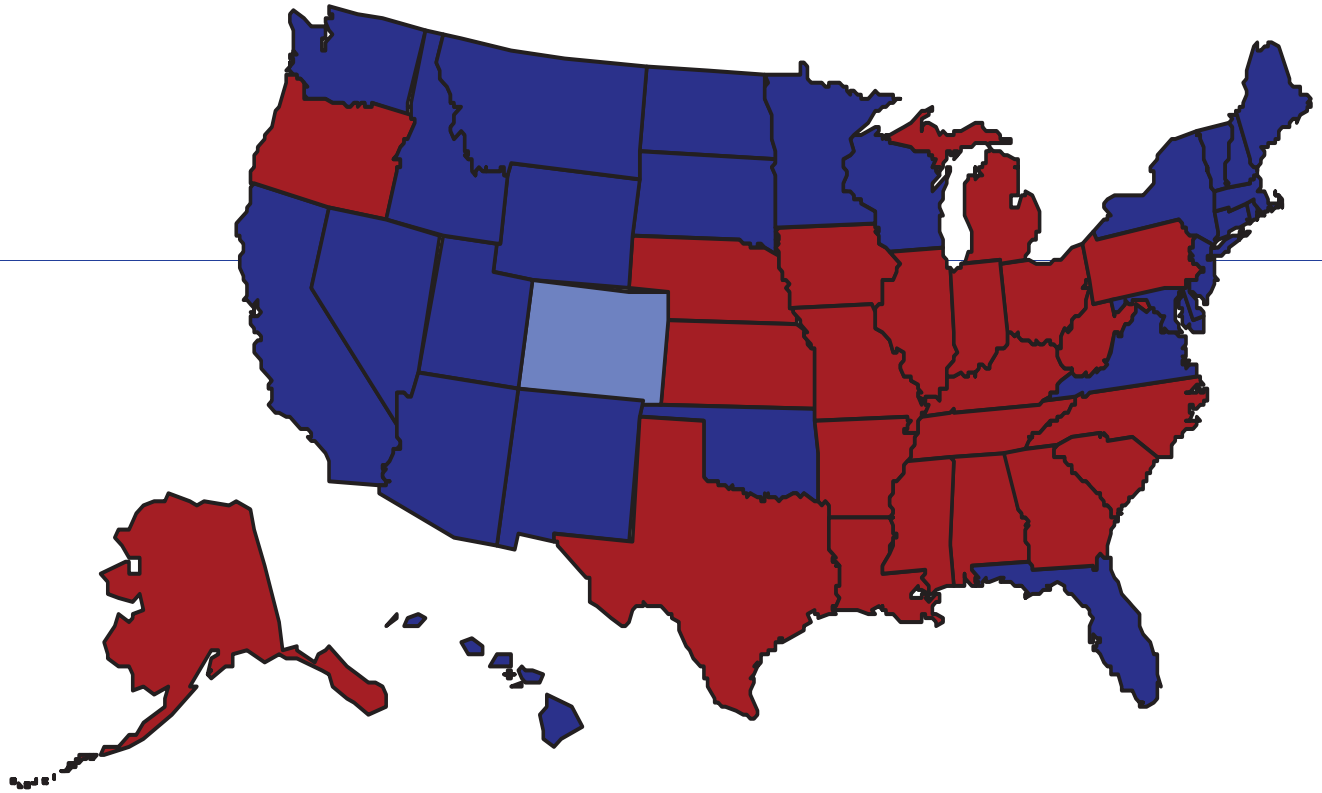
Source: Mokdad AH, et al. *J Am Med Assoc* 1999;282:16.

CDC
Centers for Disease Control and Prevention

Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



No Data | <10% | 10%-14% | 15-19% | ≥ 20%

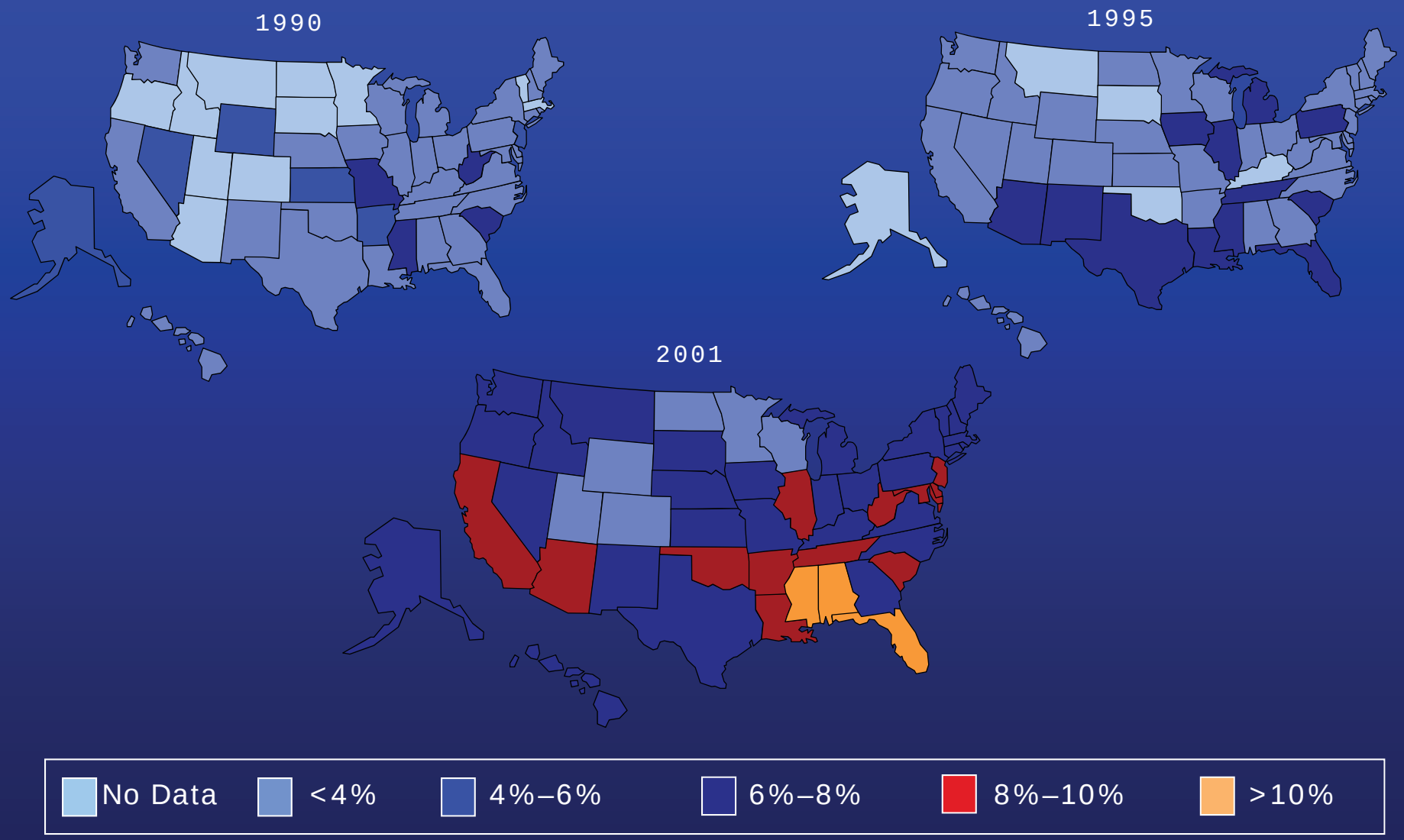
Source: Mokdad A H, et al. *J Am Med Assoc* 2001;286:10

CDC
Centers for Disease Control and Prevention

Diabetes Trends* Among Adults in the U.S.,

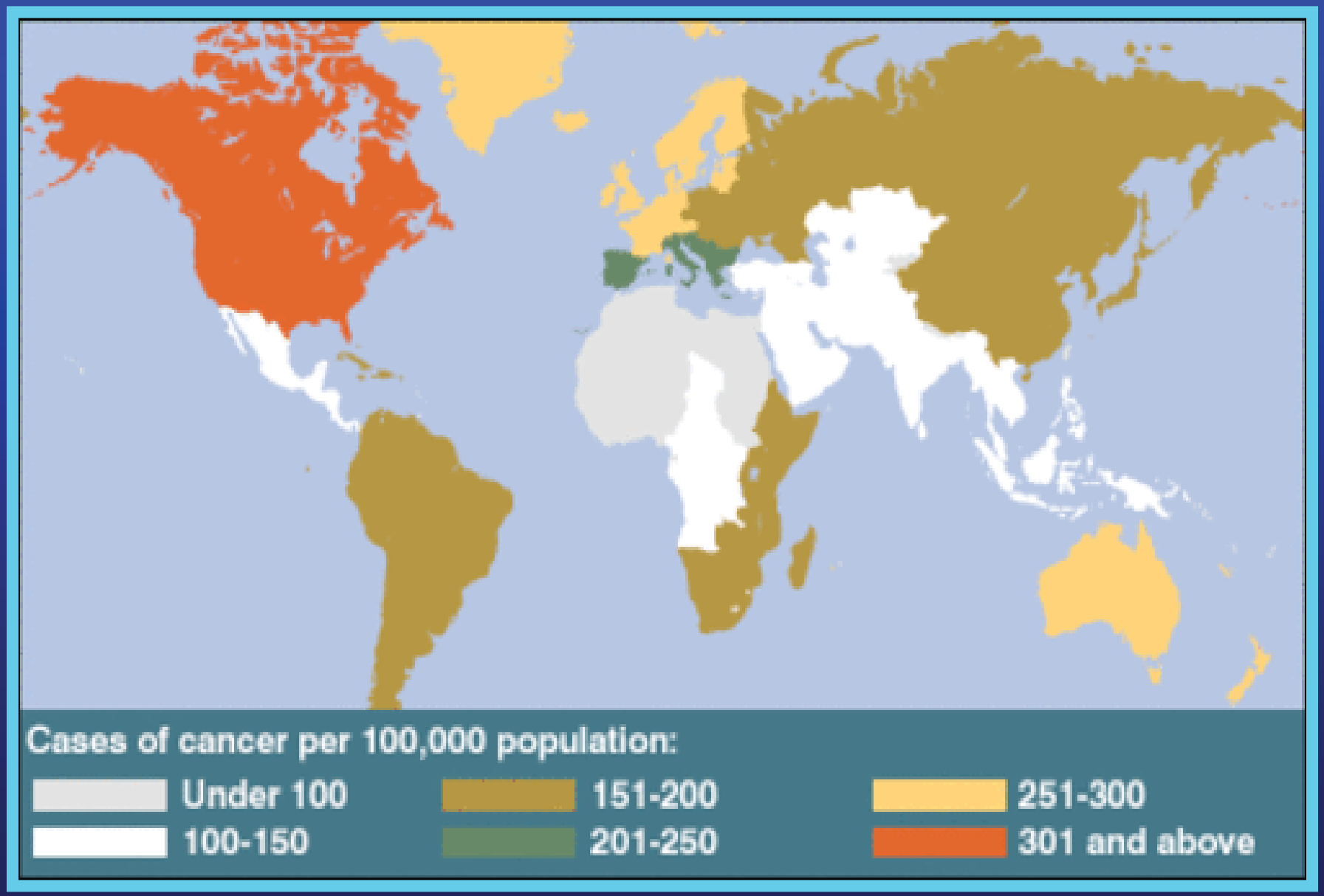
(Includes Gestational Diabetes)

BRFSS, 1990,1995 and 2001



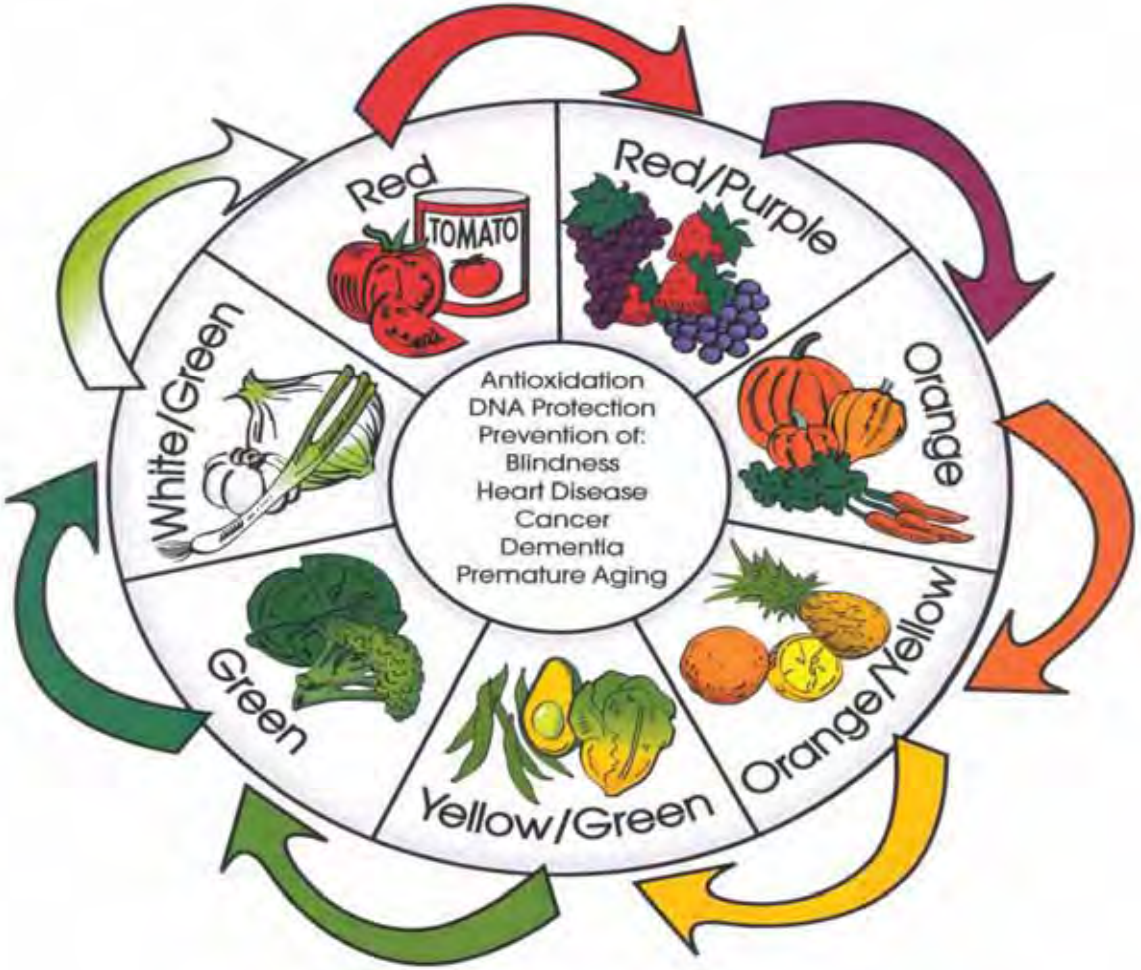
Source: Mokdad et al., *Diabetes Care* 2000;23:1278-83; *J Am Med Assoc* 2001;286:10.

Cancer Incidence Worldwide

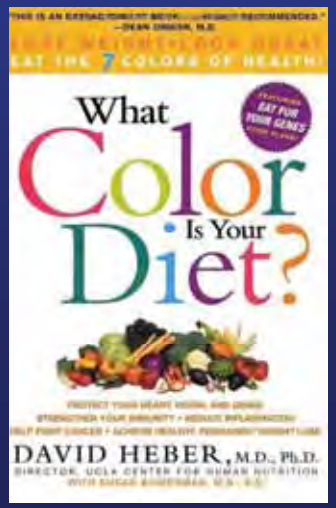


From Parkin DM, EJC, 37, 2000, 4-66

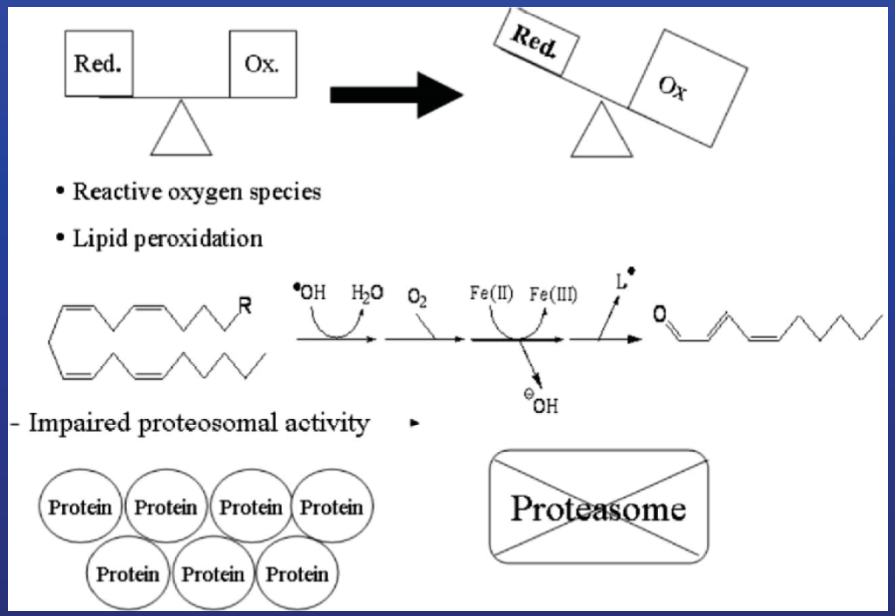
THE COLOR WHEEL OF FOODS

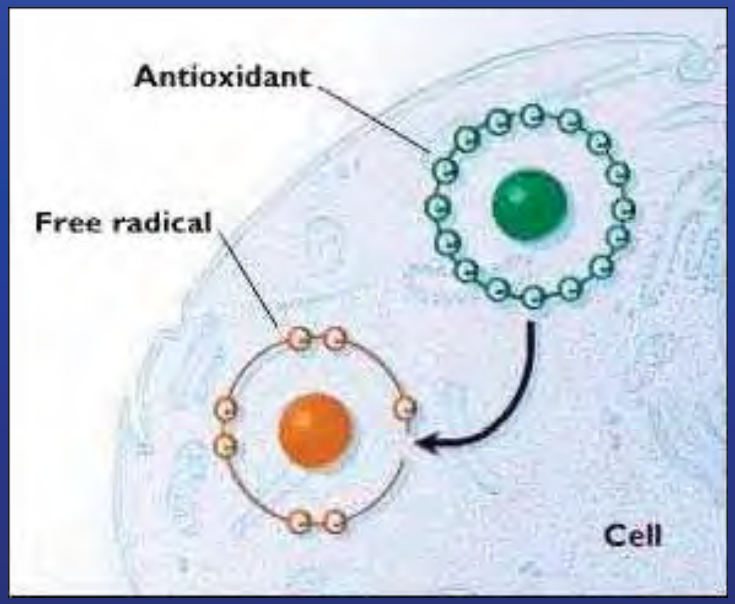


Adapted from "What Color Is Your Diet?", Harper Collins 2001



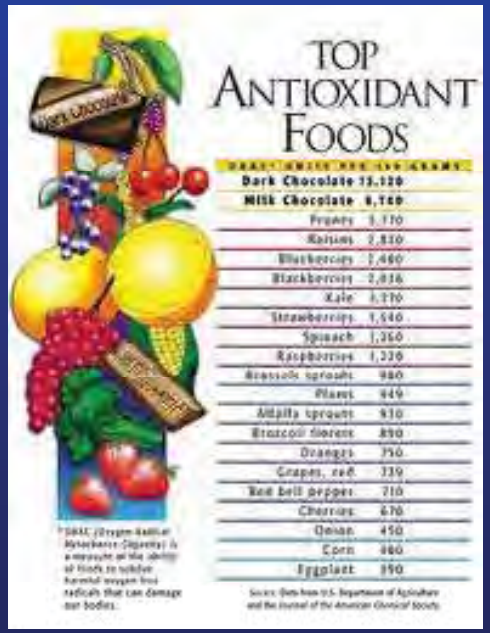
Plant Foods (Berries) are Antioxidants





Antioxidant Measures

- ORAC, DPPH, TEAC, FRAP, etc.
- Cellular tests
- Combinations



The ‘Contradictory Science of Antioxidants’

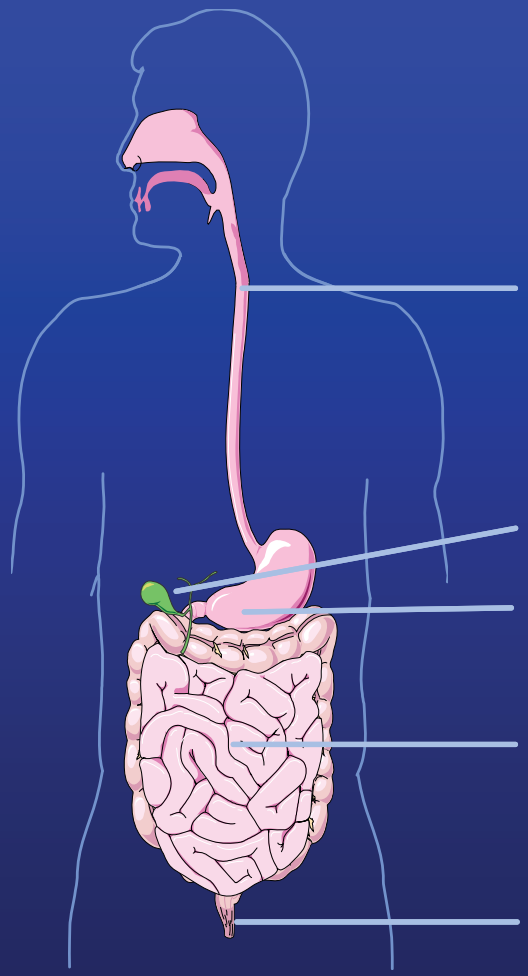
- Conflicting studies from observational studies and randomized controlled trials

In *Vitro* vs. In *Vivo*

- *In vitro* (‘test-tube’) studies commonly use high/non-physiologically achievable concentrations
- Does not always translate into *in vivo* (living) situation

In *Vitro* vs. In *Vivo*

- Absorption
- Distribution
- Metabolism
- Excretion



‘the tissue is the issue’

In Vivo Studies

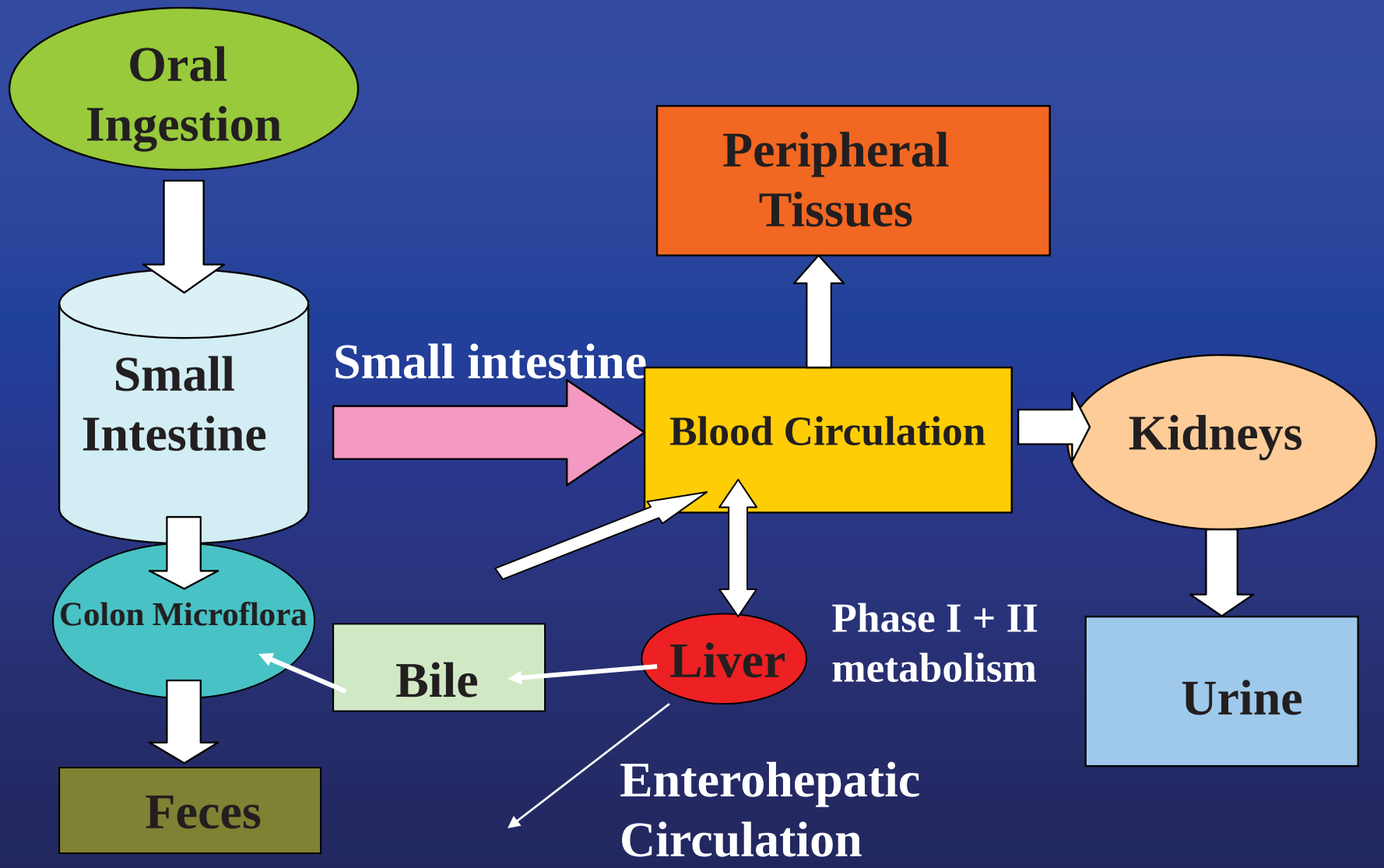
Animals: Rodents

Humans

Challenges

- Analytical challenges in estimation of levels in biological fluids and tissue
- Limited human tissue bioavailability data available : animal = human?
- Lack of correlation with blood/tissue levels and bio-activities relevant to disease states

Berry Polyphenol Metabolism



Phase II Conjugation: Glucuronidation; Sulfation; Methylation

Issues in Evaluating Polyphenol Bioavailability

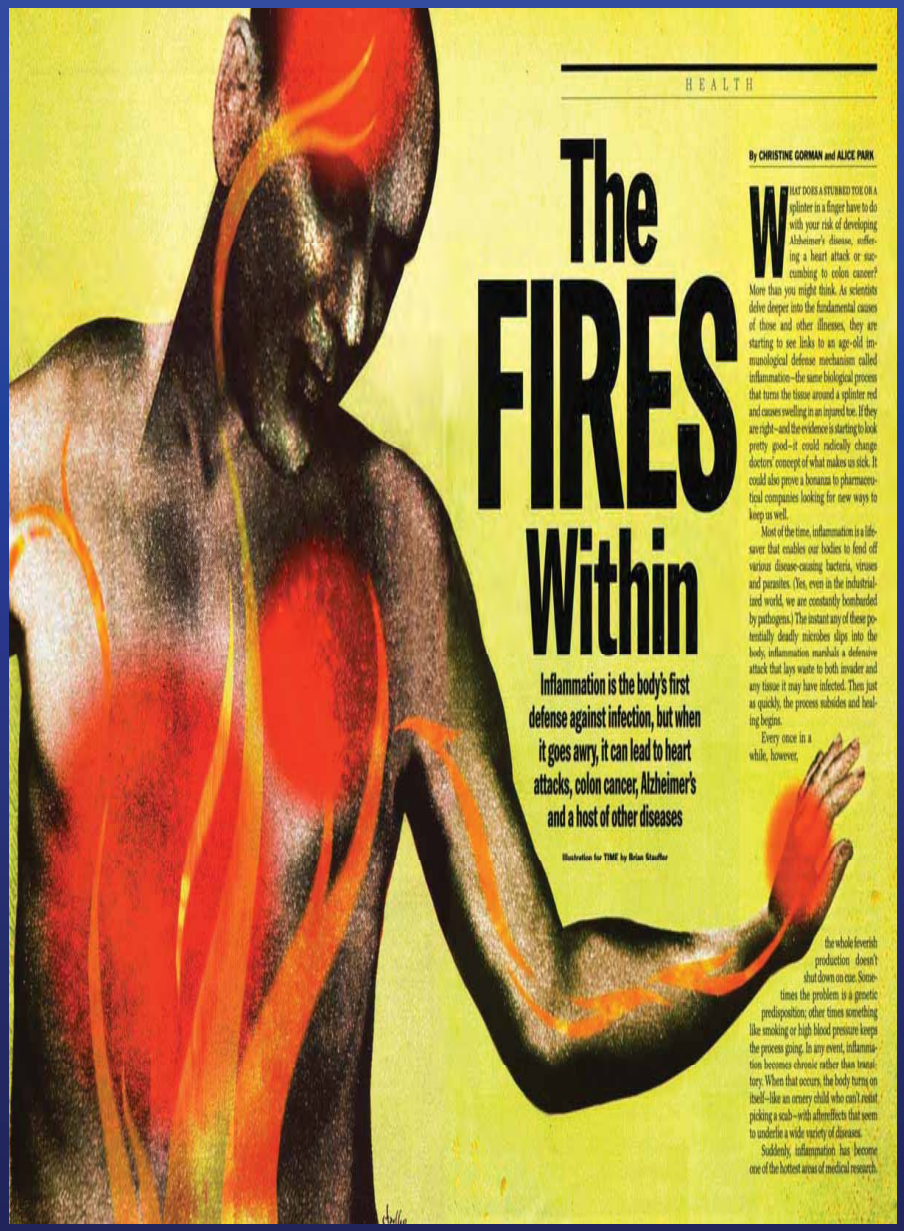
- Chemical sub-class:
  - Type and extent of food processing
- Food matrix, stability, digestive release and solubility
- Food pairings
- Metabolism : Phase 1 & 2
- Inter-individual variability:
  - Genetic polymorphisms, Gut microflora

Beyond …….Antioxidant

- Anti-Inflammatory
- Anti-neurodegenerative
- Anti-cancer
- Cardiovascular disease
- Effects on enzyme metabolizing pathways, signaling transduction pathways etc.

Seeram NP and Heber D. Impact of berry phytochemicals on human health: Effects beyond antioxidation. Chapter 21.; American Chemical Society (ACS) Symposium Series No. 956l; Oxford University Press, UK, 2006.

Inflammation & Disease



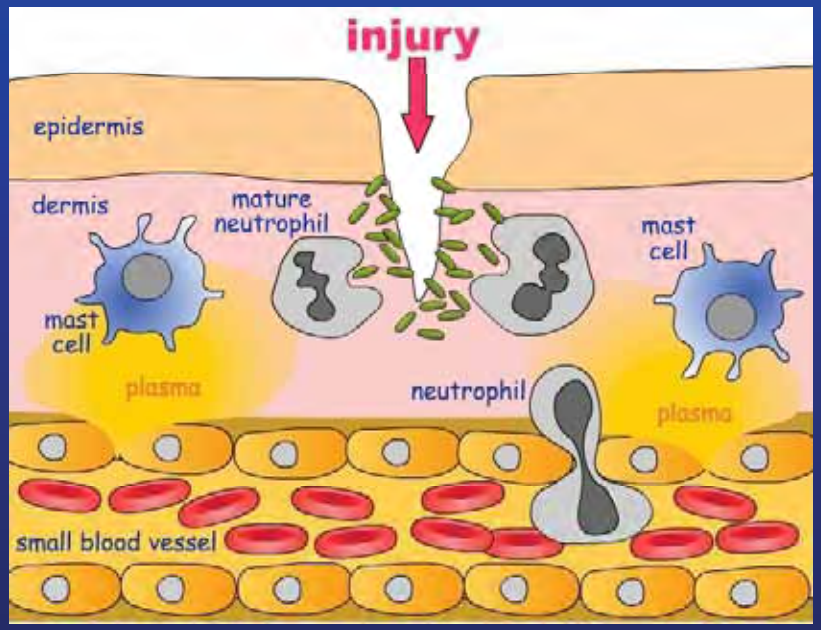
TIME Feb. 23, 2004

What is Inflammation?

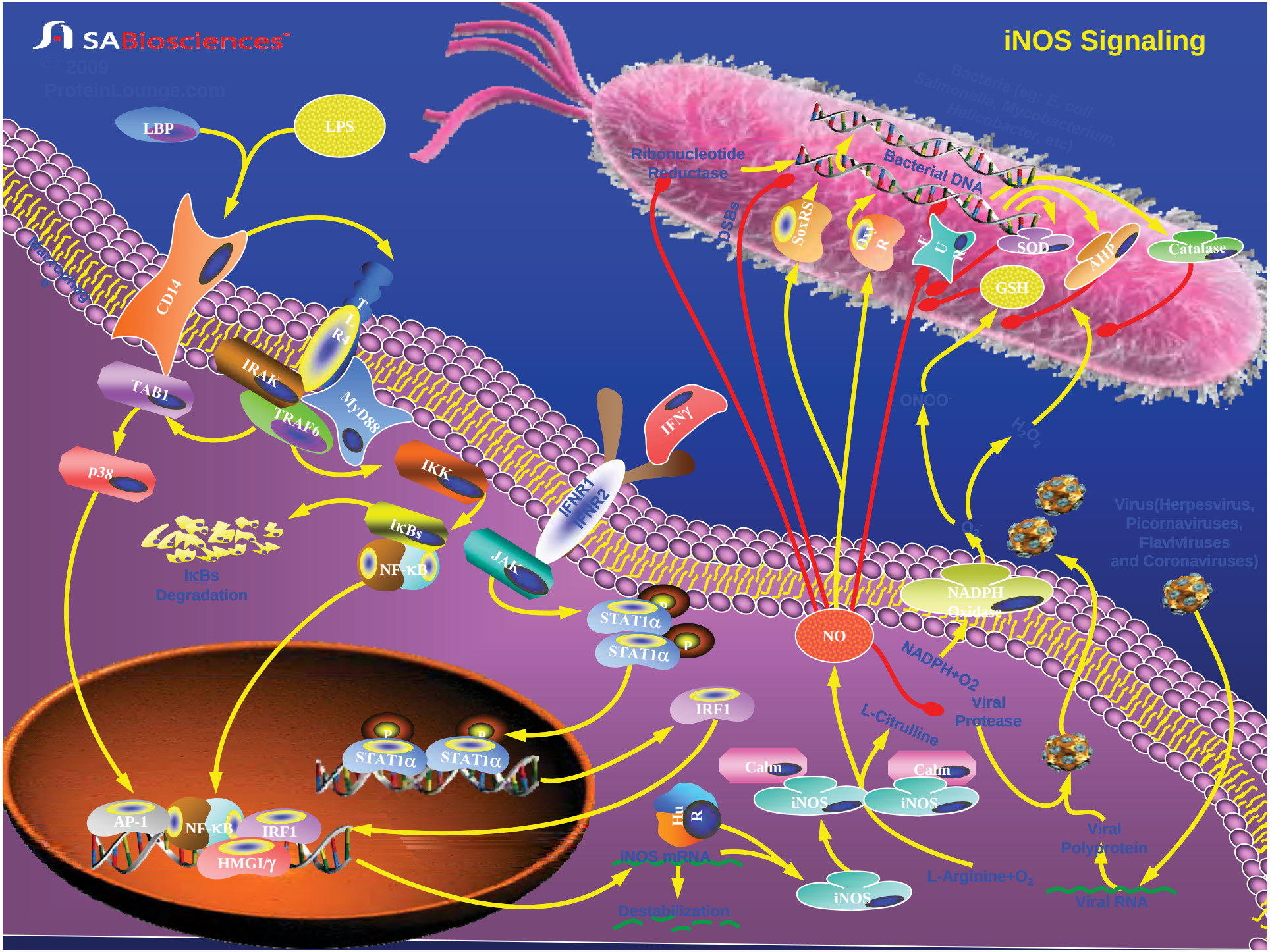
- Inflammation is an immune response to injury or infection causing pain, redness, heat, and swelling in the affected area.

- Two types:
  - Acute Inflammation
  - Chronic Inflammation

- Causes of Inflammation
  - Trauma
  - Endogenous antigens
  - Chemical agents
  - Microbial pathogens



Cells involved: Macrophages, Mast cells, Neutrophils, Lymphocytes, etc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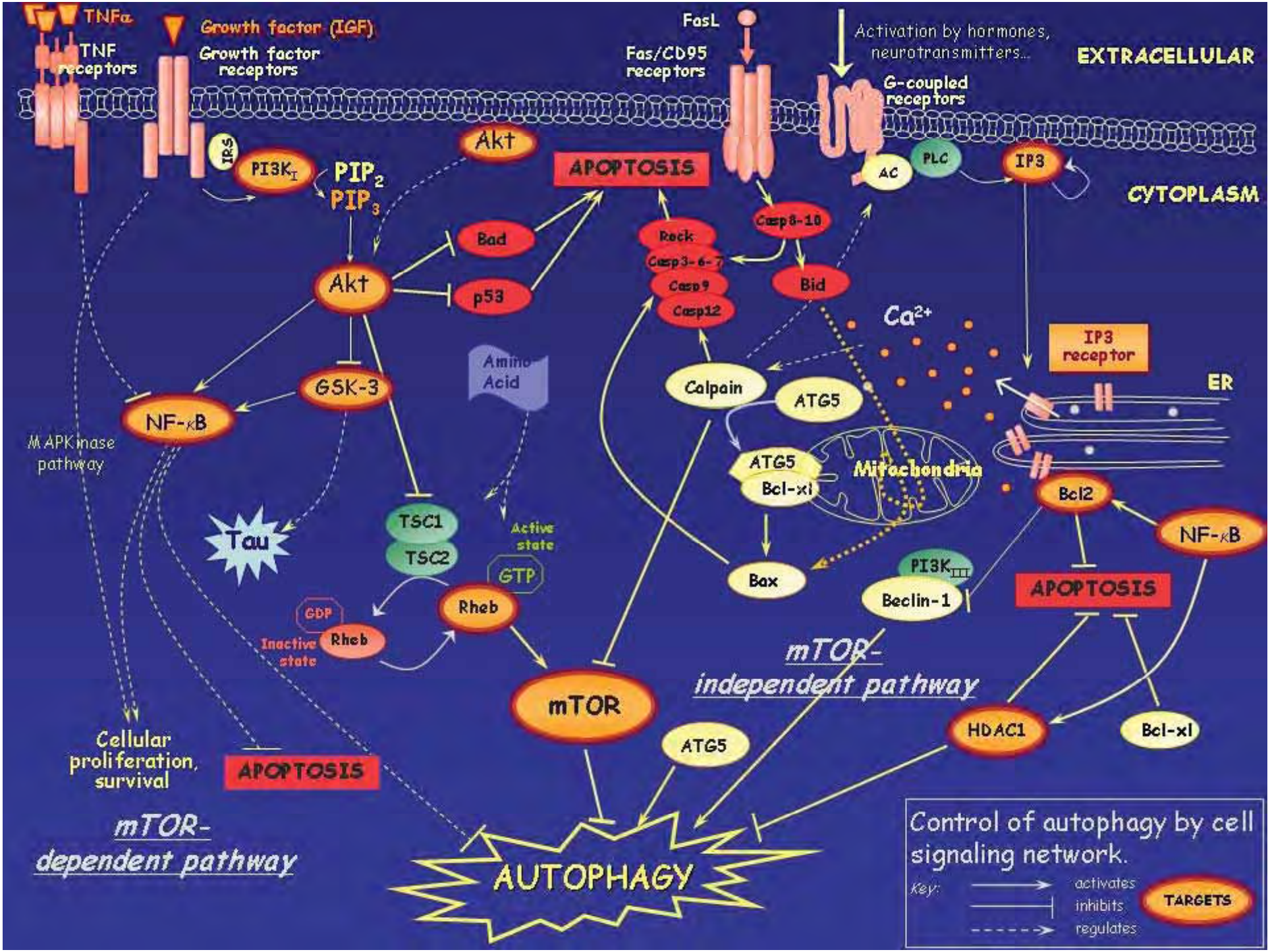
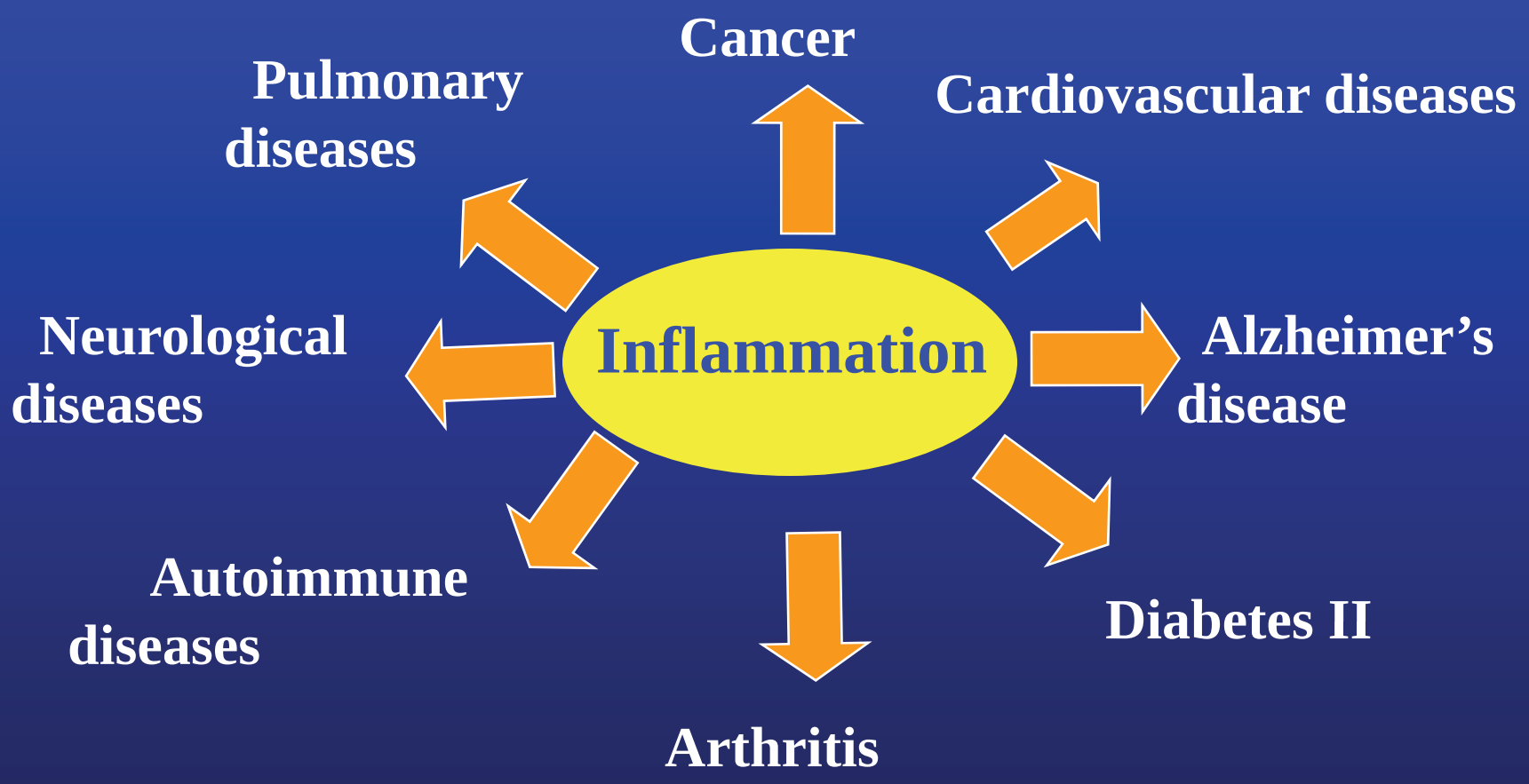
ProteinLounge.com
iNOS Signaling
LBP
LPS
CD14
TLR4
MyD88
IRAK
TRAF6
TAB1
p38
IKK
IκBs
NF-κB
IκBs
Degradation
JAK
IFNR1
IFNR2
IFNγ
STAT1α
STAT1α
P
P
STAT1α
STAT1α
AP-1
NF-κB
IRF1
HMGI/γ
IRF1
Ribonucleotide
Reductase
Bacterial DNA
dDSBs
SoxRS
OxyR
FUR
SOD
AHP
Catalase
GSH
Bacteria (eg: E. coli
Salmonella, Mycobacterium,
Helicobacter, etc)
Neutrophils
ONOO-
H2O2
O2-
Virus(Herpesvirus,
Picornaviruses,
Flaviviruses
and Coronaviruses)
NADPH
Oxidase
NO
NADPH+O2
Viral
Protease
L-Citrulline
Calm
Calm
iNOS
iNOS
iNOS
Hu
R
iNOS mRNA
Destabilization
L-Arginine+O2
Viral
Polyprotein
Viral RNA

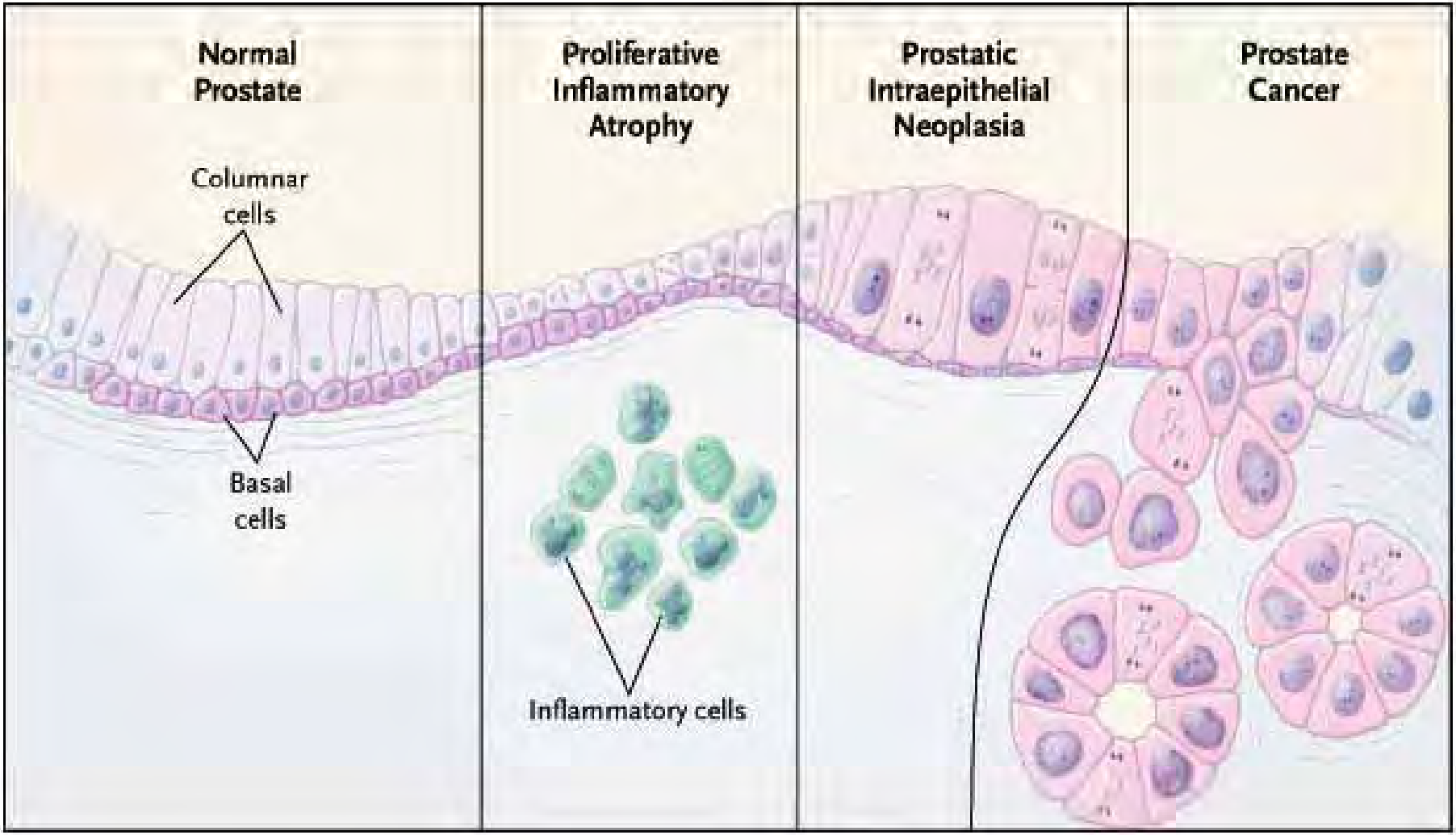

TNFα
TNF receptors
Growth factor (IGF)
Growth factor receptors
FasL
Fas/CD95 receptors
Activation by hormones, neurotransmitters...
G-coupled receptors
EXTRACELLULAR
CYTOPLASM
IRS
PI3K$_I$
PIP$_2$
PIP$_3$
Akt
APOPTOSIS
AC
PLC
IP3
Bad
p53
Rock
Casp3-6-7
Casp9
Casp12
Casp8-10
Bid
Ca^{2+}
IP3 receptor
ER
Amino Acid
GSK-3
NF-κB
Calpain
ATG5
MAPKinase pathway
ATG5
Bcl-xl
Mitochondria
Bcl2
NF-κB
Tau
TSC1
TSC2
Active state
GTP
Rheb
GDP
Inactive state
Rheb
Bax
PI3K$_{III}$
Beclin-1
APOPTOSIS
mTOR-independent pathway
mTOR
ATG5
HDAC1
Bcl-xl
Cellular proliferation, survival
APOPTOSIS
mTOR-dependent pathway
AUTOPHAGY
Control of autophagy by cell signaling network.
Key:
activates
inhibits
regulates
TARGETS

Inflammation linked to most diseases



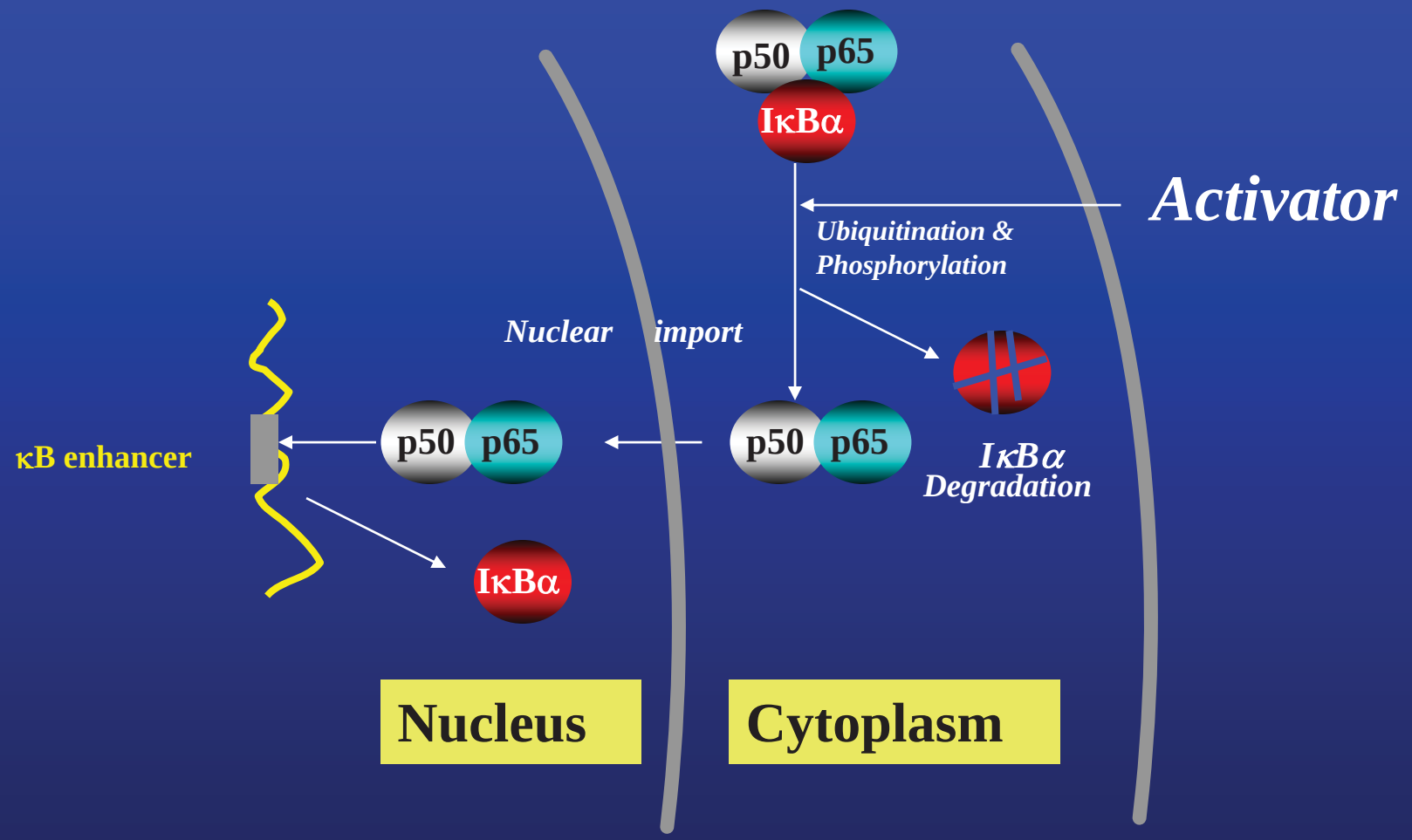
Inflammation and CaP

Proliferative Inflammatory Atrophy: Possible precursor to CaP



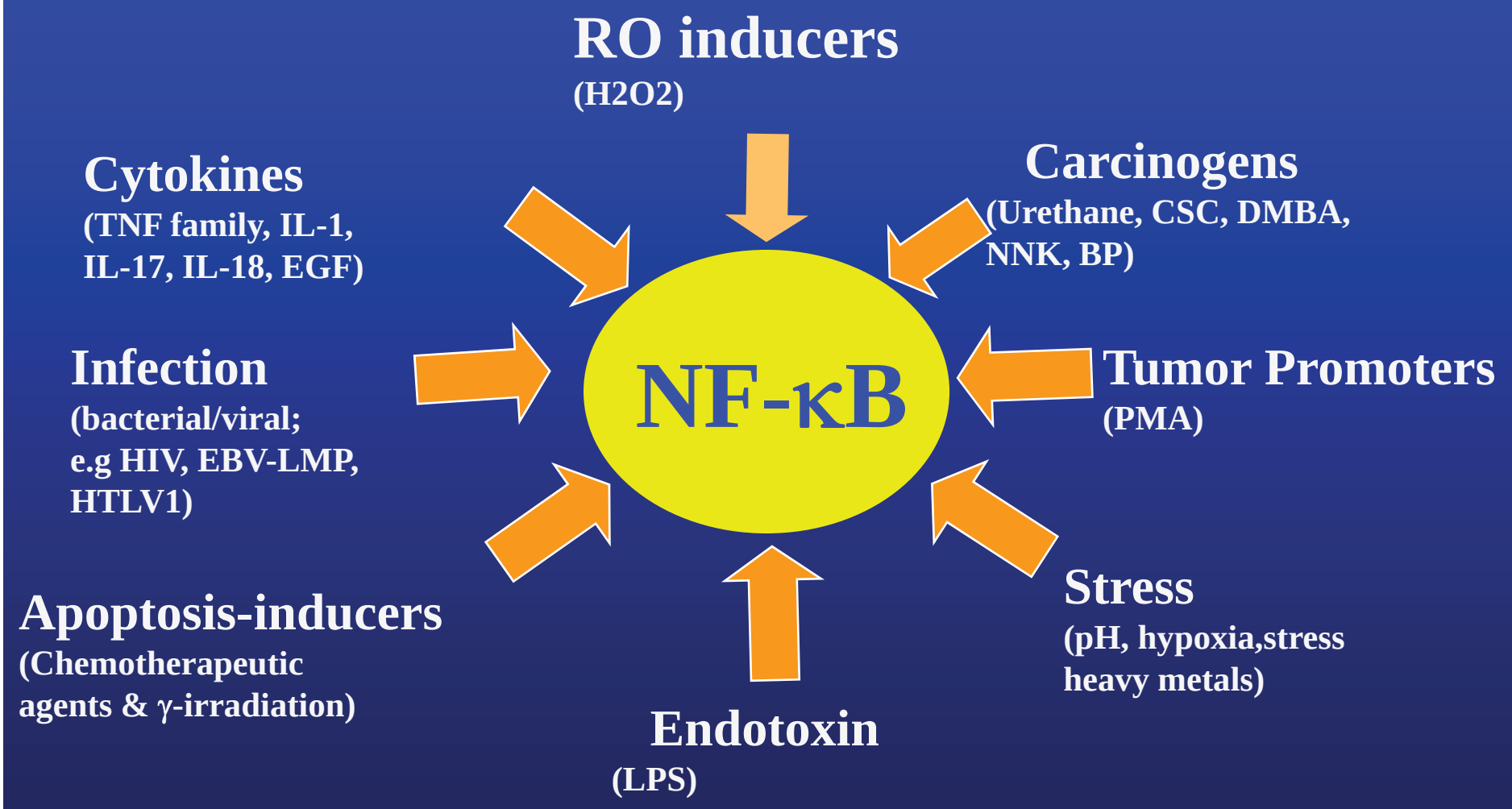
Nelson W.G. et al. New Engl. J. Med., 2003, 349, 366-81.

Nuclear Factor Kappa Beta (NF-κB)



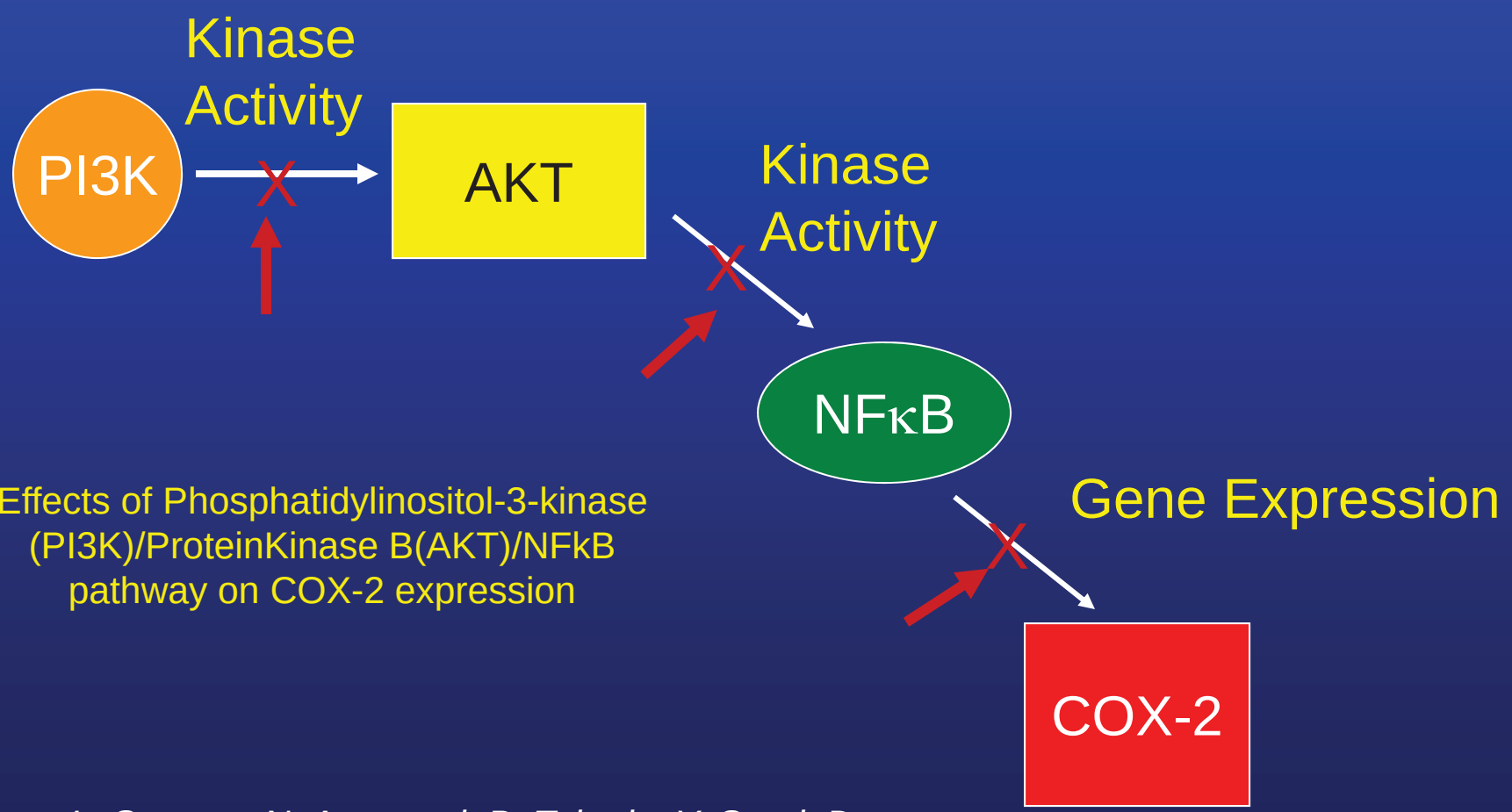
Garg and Aggarwal, Leukemia, 2002

What activates NF-κB?



Aggarwal BB, Cancer Cell, 2004

Berry Polyphenols Inhibit Pro-Inflammatory Cell Signaling *In Vitro*



Effects of Phosphatidylinositol-3-kinase (PI3K)/ProteinKinase B(AKT)/NFkB pathway on COX-2 expression

Adams, L; Seeram, N; Aggarwal, B; Takada, Y, Sand, D; Heber, D. J. Agric. Food Chem. 2006, 54, 980-985

Research Directions

- Probe for mechanistic insights into anti-inflammatory at cellular levels
  - At the ‘cytokine’ and ‘gene expression’ level, As direct inhibitors of COX-2 and iNOS, etc.
  - Regulatory pathways and sub-cellular signaling

Berry Science & Marketing

Inflammation and Oxidative Stress are Associated With Chronic Disease

Single BerryCompounds Reduce Inflammation and Oxidative Stress

Combinations of Berry Compounds Reduce Inflammation and Chronic Disease Risk

QUESTIONS?

Email: nseeram@uri.edu