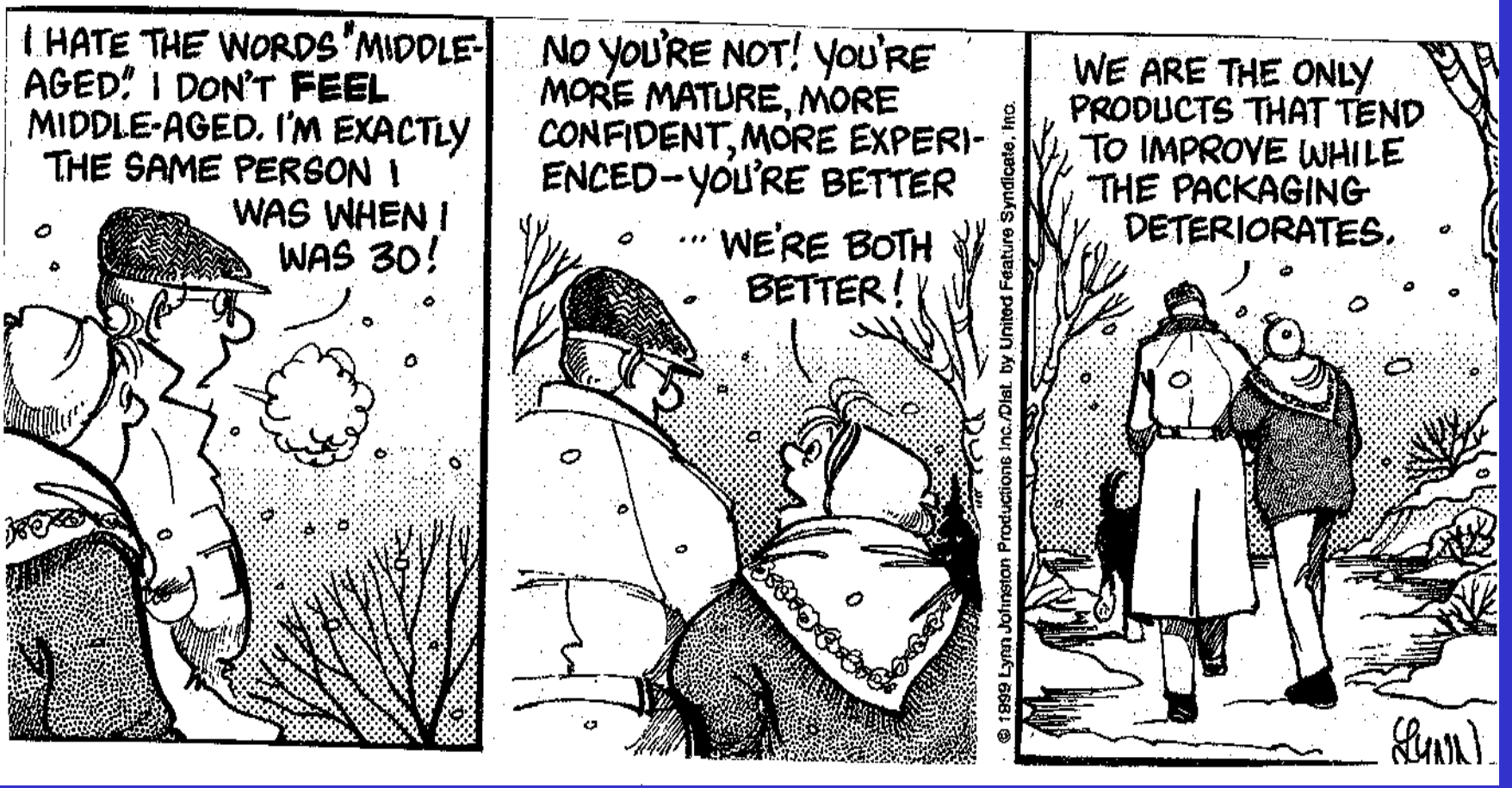
Overview of Age-Related Changes in Physiology

Tamara Harris, M.D., M.S.
Laboratory of Epidemiology, Demography and Biometry
National Institute on Aging


I HATE THE WORDS "MIDDLE-AGED." I DON'T FEEL MIDDLE-AGED. I'M EXACTLY THE SAME PERSON I WAS WHEN I WAS 30!
NO YOU'RE NOT! YOU'RE MORE MATURE, MORE CONFIDENT, MORE EXPERIENCED—YOU'RE BETTER ... WE'RE BOTH BETTER!
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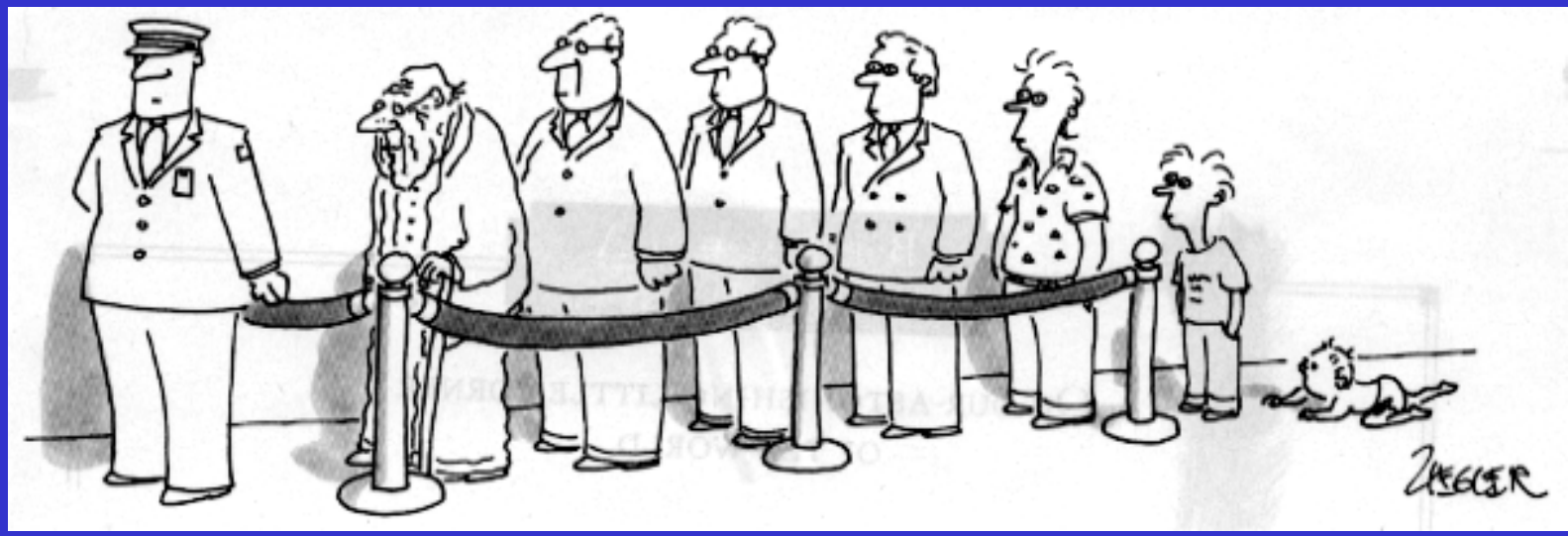
WE ARE THE ONLY PRODUCTS THAT TEND TO IMPROVE WHILE THE PACKAGING DETERIORATES.

Table 1. Physiological changes that occur with ageing and have the potential to influence drug disposition and metabolism.

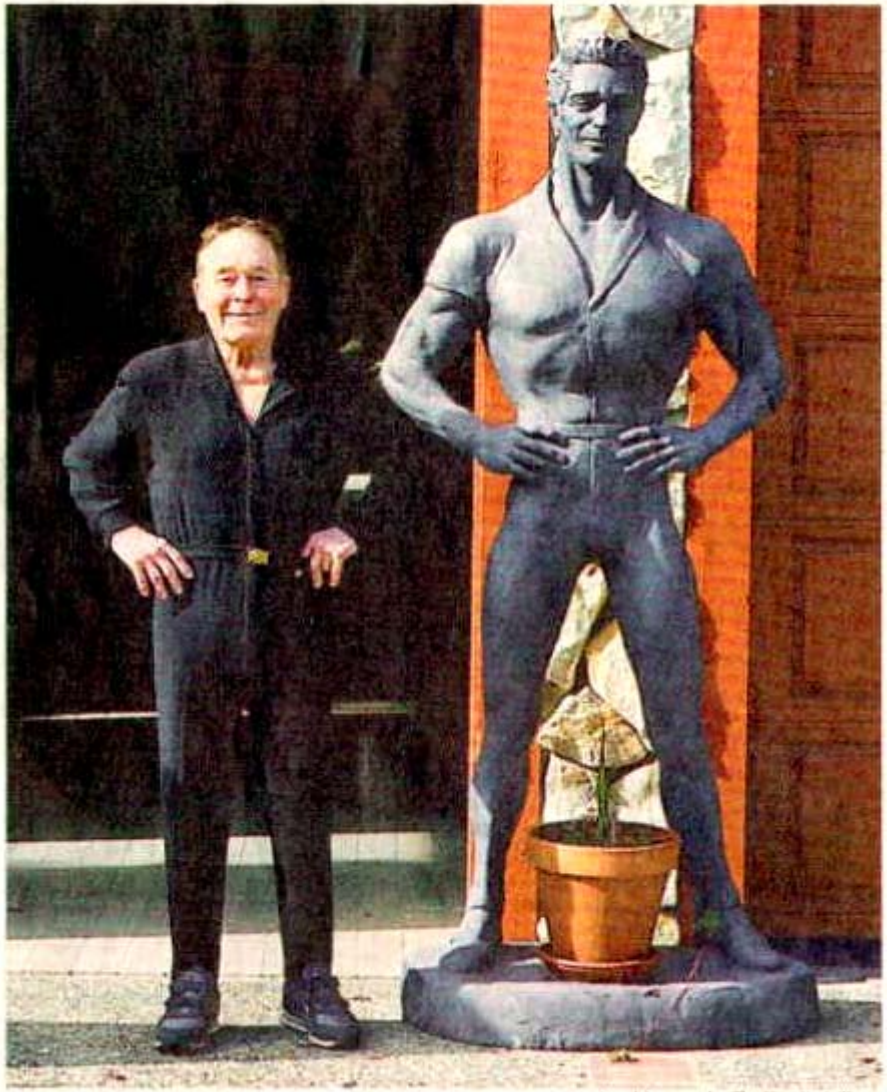
System	Change
General	Reduced total body mass
	Reduced basal metabolic rate
	Reduced proportion of body water
	Increased proportion of body fat
Circulatory	Decreased cardiac output
	Altered relative tissue perfusion
	Decreased plasma protein binding
Gastrointestinal	Reduced gastric acid production
	Reduced gastric emptying rate
	Reduced gut motility
	Reduced gut blood flow
	Reduced absorption surface
	Intestinal uptake/transport?
	Intestinal metabolism(?)
Hepatic-biliary	Reduced liver mass
	Reduced liver blood flow
	Reduced albumin synthesis
	Hepatic and biliary uptake/transport?



Weight and height tend to increase with age, then decrease

Body fat increases even if weight is constant
Central fat, particularly visceral fat, increases with age
Lean mass decreases with age as does bone
Both tissues are increasingly infiltrated with fat with age

Ageless Apostle of Muscle



Ann Johansson for The New York Times

Jack LaLanne, beside a statue of himself outside his home in Morro Bay, Calif., attributes his vigor at age 88 to a lifetime of exercise and his good eating habits.

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Hepatic-biliary	Reduced liver mass Reduced liver blood flow Reduced albumin synthesis Hepatic and biliary uptake/transport?

Table 2. Human cytochrome P450 (CYP) superfamily.

Most important CYP-isoforms	Abundance in liver (%)†	% of drugs metabolized‡
CYP3A4	30	52
CYP2C proteins	20	20
CYP1A2	13	11
CYP2E1	7	7.5
CYP2A6	4	1.2
CYP2D6	2	25
Other CYPs	ca. 25	2.5

†Data taken from Shimada *et al.*[21]
‡Based on 170 characterized xenobiotics.

Table 3. Important cytochrome P450s (CYP) involved in human drug metabolism and their typical substrates (probe drugs).

CYP-isoforms	Examples of model drugs
1A2	Caffeine, theophylline
2C9	Diclofenac, ibuprofen, phenytoin, tolbutamide, S-warfarin
2C19	Mephenytoin, omeprazole (+ 3A4), diazepam (+ 3A4)
2D6	Debrisoquine, sparteine, dextromethorphan, amitriptyline, codeine, propafenone (+ 3A, 1A2 and phase II)
2E1	Chlorzoxazone, halothane, paracetamol (+ conjugation)
3A3/4	Cyclosporine, erythromycin, lidocaine, midazolam, nifedipine, verapamil (+ 1A2, 2C)

BUT!!

Few consistent problems secondary to age-related liver changes

Renal function declines with age

Can be estimated from serum creatinine

Exacerbated by hypertensive disease

May affect clearance of supplements

BUT!!

Few consistent problems identified

Little known about effects of non-alcoholic fatty liver

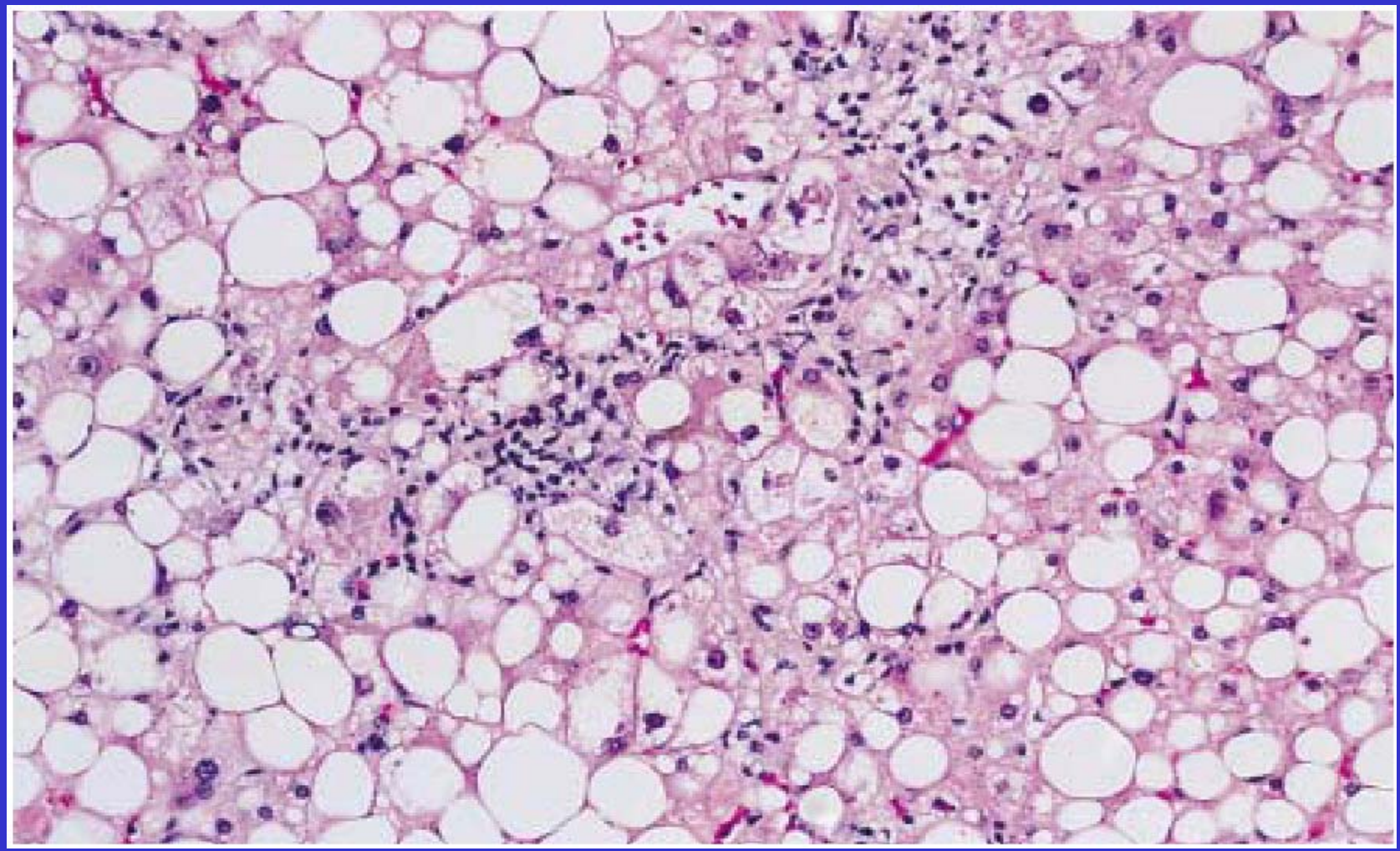


TABLE 1. CAUSES OF FATTY LIVER DISEASE.

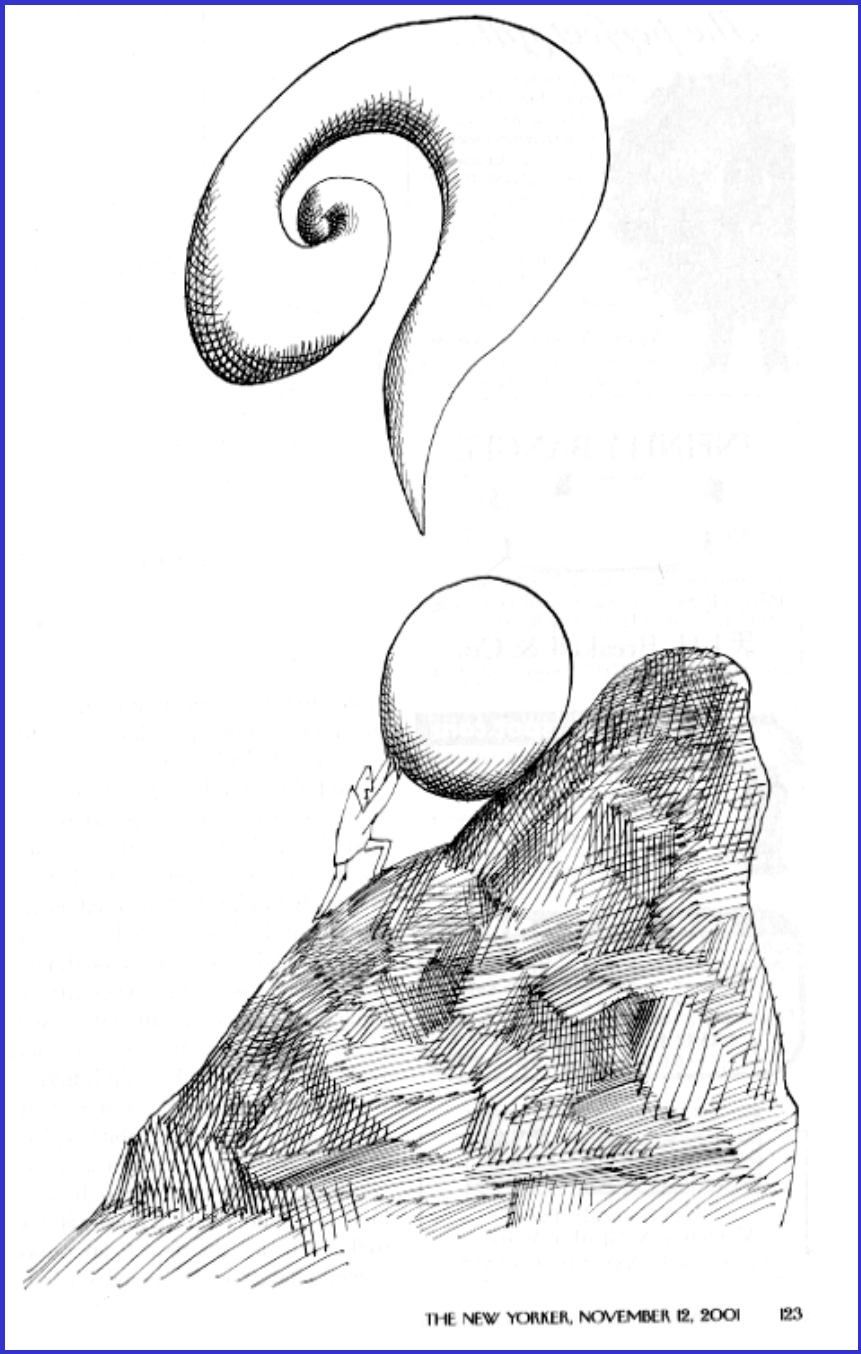
NUTRITIONAL	DRUGS*	METABOLIC OR GENETIC	OTHER
Protein-calorie malnutrition†	Glucocorticoids†	Lipodystrophy†	Inflammatory bowel disease†
Starvation†	Synthetic estrogens†	Dysbetalipoproteinemia†	Small-bowel diverticulosis with bacterial overgrowth†
Total parenteral nutrition†	Aspirin‡	Weber–Christian disease†	Human immunodeficiency virus infection†
Rapid weight loss†	Calcium-channel blockers†	Wolman's disease§	Environmental hepatotoxins
Gastrointestinal surgery for obesity†	Amiodarone§	Cholesterol ester storage§	Phosphorus‡
	Tamoxifen†	Acute fatty liver of pregnancy‡	Petrochemicals†‡
	Tetracycline‡		Toxic mushrooms†
	Methotrexate†		Organic solvents
	Perhexiline maleate§		*Bacillus cereus* toxins‡
	Valproic acid‡		
	Cocaine‡		
	Antiviral agents		
	Zidovudine†		
	Didanosine‡		
	Fialuridine‡		

*This is a partial list of agents that produce fatty liver. Some drugs produce inflammation as well. The association of fatty liver with calcium-channel blockers and valproic acid is weak, whereas the association with amiodarone is strong. Drug-induced fatty liver may have no sequelae (e.g., cases caused by glucocorticoids) or can result in cirrhosis (e.g., cases caused by methotrexate and amiodarone).

†This factor predominantly causes macrovesicular steatosis (mostly owing to imbalance in the hepatic synthesis and export of lipids).

‡This factor predominantly causes microvesicular steatosis (mostly owing to defects in mitochondrial function).

§This factor causes hepatic phospholipidosis (mostly owing to the accumulation of phospholipids in lysosomes).



Major age-related problem is due to lack of communication:

Patients don't tell their health care provider they are taking supplements unless the health care provider asks!

Why don't patients tell?

- **doctors are prejudiced or not knowledgable**
- **don't want to admit to unconventional therapies**
- **reason for use seen as unrelated to care**
- **not consider supplements to be "drugs"**

Other factors mentioned in earlier presentations….

Herbal Medicines and Perioperative Care

Ang-Lee et al. JAMA 2001;286:208

Echinacea – Immunosuppressive
Hepatotoxic

Ephedra -- Sympathomimetic
Half-life 5 hours – urine-excreted

Garlic -- Platelet function
Stop 7 days prior to surgery

Gingko -- Platelet function among others
Stop 36 hours prior to surgery

Herbal Medicines and Perioperative Care

Ang-Lee et al. JAMA 2001;286:208

Ginseng -- Platelet function among others
Stop 7 days before surgery

Kava -- Sedative/hypnotic
Half-life 9 hours –urine/feces
Stop 24 hours before surgery

Valerian -- Sedative-GABA receptor drugs
potentiated - ?withdrawal

Table 6. Pharmacodynamic drug interactions.

Object drug	Precipitant drug	Consequence
A. Direct pharmacodynamic drug interactions		
Verapamil	β adrenoceptor antagonists	Arrhythmia, asystole, heart failure
Warfarin	Clofibrat	Increased anti-coagulation
	Corticosteroids	
	Anabolic steroids	
	Oestrogens	
	Tetracyclines	
Coumarins	Vitamin K_1	Reduced anti-coagulation
Centrally acting drugs	Centrally acting drugs	Potentiation of CNS-depressant effect
Opiate analgesics	Naloxone	Reversal of opiate effects
Depolarizing muscle relaxants	Quinidine	
	Aminoglycosides	Increased skeletal muscle relaxation
B. Indirect pharmacodynamic drug interactions		
Amiodarone	Class I anti-arrhythmic drugs	Arrhythmia
Cardiac glycosides	Drugs causing hypercalcaemia	Increased cardiac effect
Cardiac glycosides	Drugs causing potassium loss	Risk of arrhythmia
Angiotensin converting enzyme-inhibitors	Vasodilators	Increased hypotensive effect
Anti-coagulants	Fibrinolytic drugs	Risk of bleeding
Anti-coagulants	Drugs causing gastrointestinal ulceration	Risk of bleeding
Diuretics	Drugs causing fluid retention	Increased diuretic effect
Hypnotics	Ethanol	Decreased vigilance, respiratory depression, coma
Serotonin re-uptake inhibitors	St. John's wort	
	Monoamine oxidase inhibitors	Headache, tremor, restlessness, convulsion (serotonin syndrome)
Aminoglycosides	Loop diuretics	Increased nephrotoxicity and ototoxicity

For a review, see Seymour & Routledge.[107]

St. John's wort – putative antidepressant

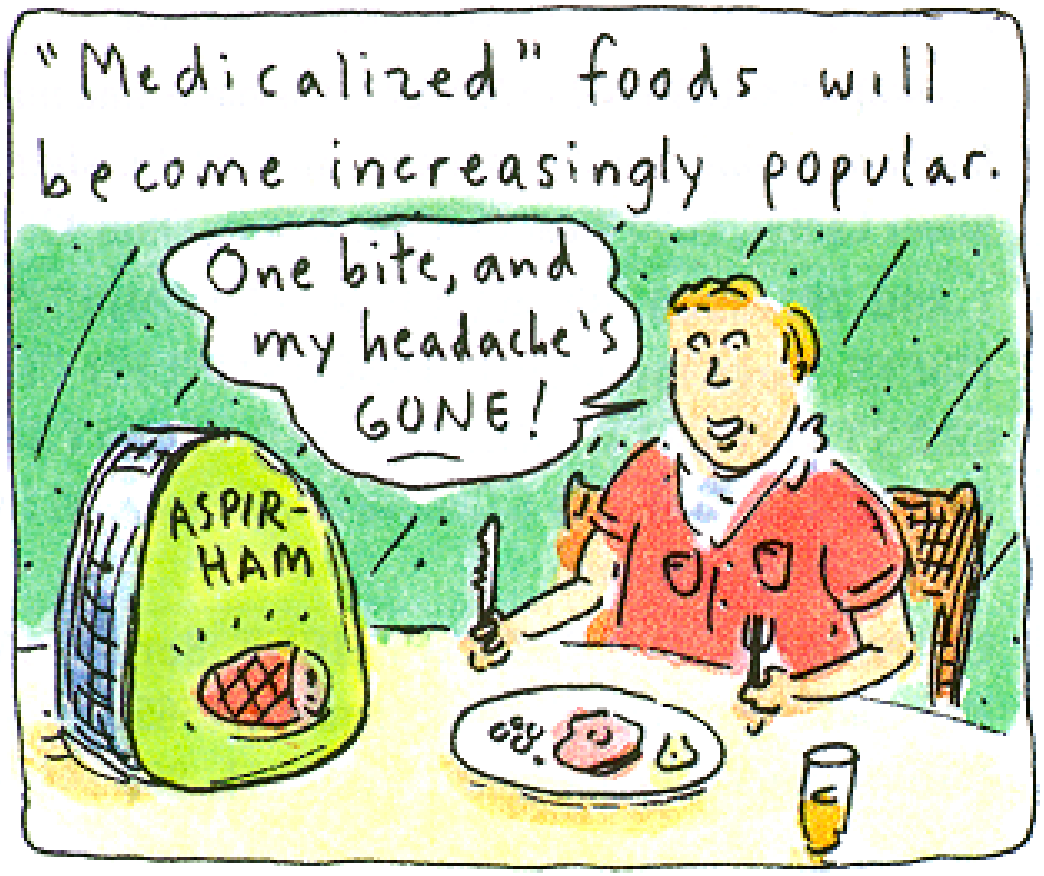
- Liver function
- CYP4503A4 induced – doubling metabolic activity
  - Lidocaine, calcium channel blockers, serotonin receptor antagonists
- CYP4502C9 induced -- reduces anticoagulant effects of warfarin, interferes with other NSAIDS

Where do people get their information?

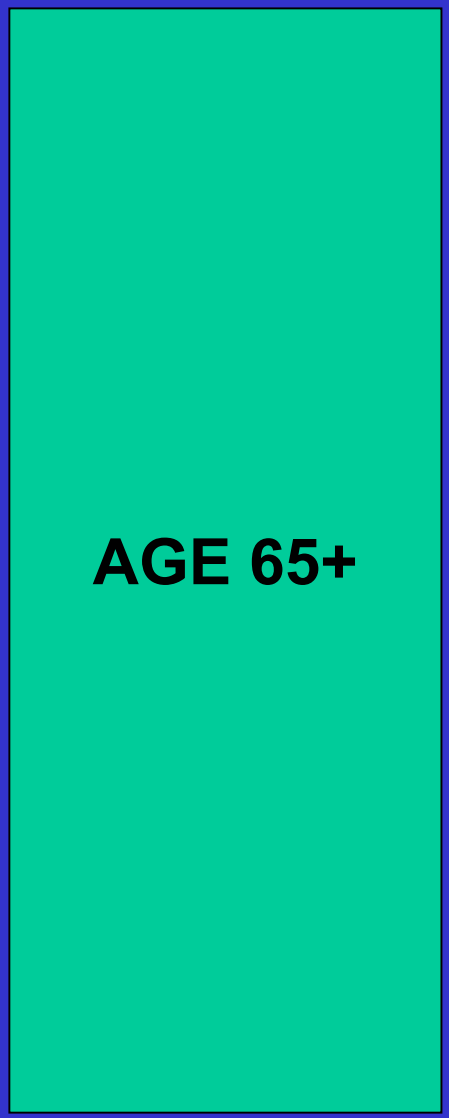
Table 1. Content Quality of 208 Websites (URLs) with Information about St. John's Wort

Evaluated Criteria Question (κ Value)	Number (%)
1. Are drug interactions mentioned? (0.54)	
a) Wrong drugs mentioned or statement "no interactions present"	8 (4)
b) No	154 (74)
c) Yes, at least one correct drug explicitly mentioned	46 (22)
2. Are consequences of pharmacokinetic drug interactions mentioned? (1.00)	
a) No	201 (97)
b) Yes, decreased effect of interacting drug	5 (2)
c) Yes, decreased effect of interacting drug and any correct recommendation how to proceed	2 (1)
3. Are consequences of pharmacodynamic drug interactions with antidepressants mentioned? (0.46)	
a) No	169 (81)
b) Yes	7 (3)
c) Yes, and any correct recommendation how to proceed	32 (15)
4. Is only the correct indication of depression mentioned? (0.57)	
a) No, other indications than depression mentioned	141 (68)
b) No indication mentioned at all	22 (11)
c) Yes, only depression mentioned	45 (22)

URL = uniform resource locator.

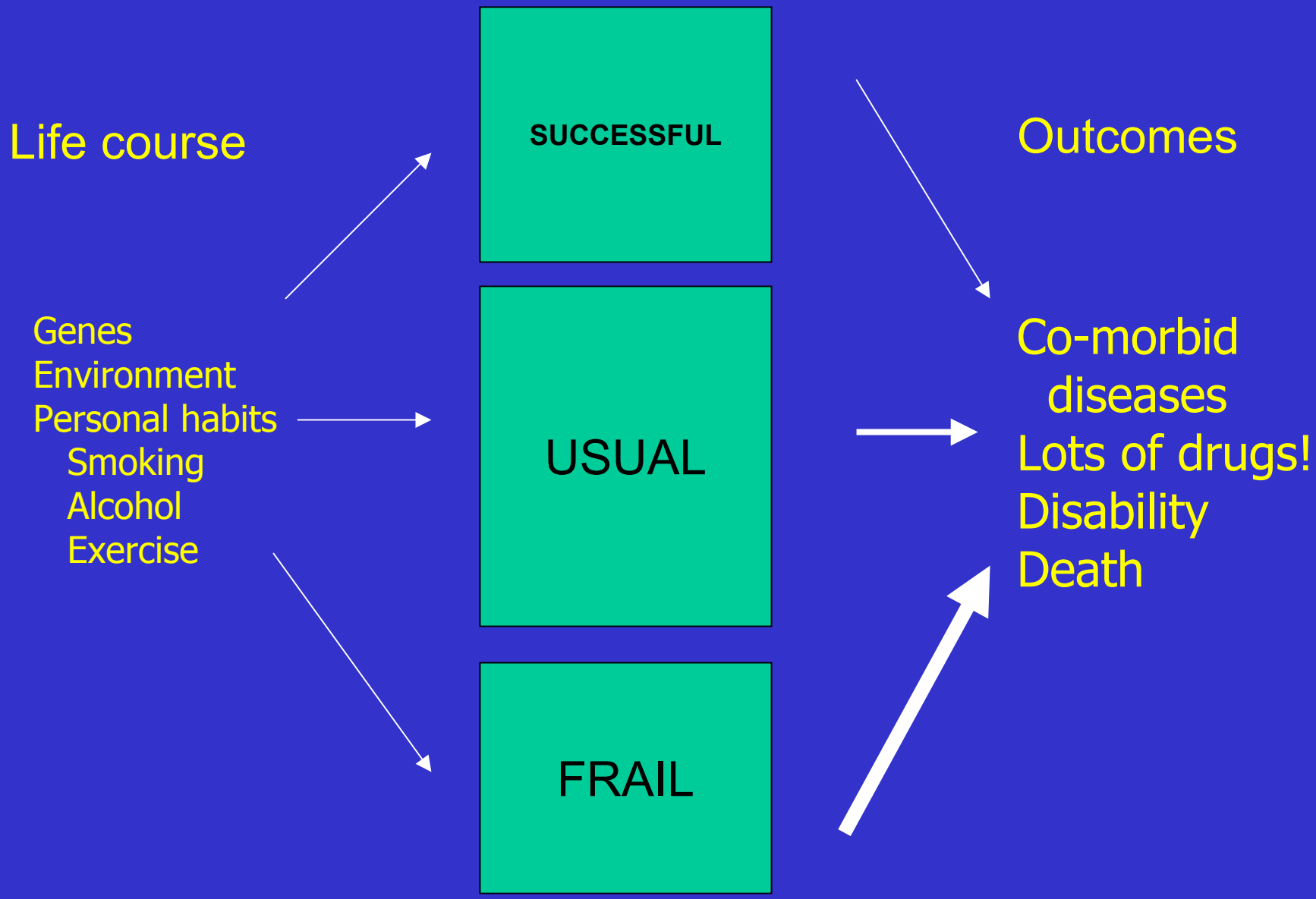

"Medicalized" foods will become increasingly popular.
One bite, and my headache's GONE!
ASPIR-HAM

AGING TODAY: Homogeneity VERSUS Heterogeneity



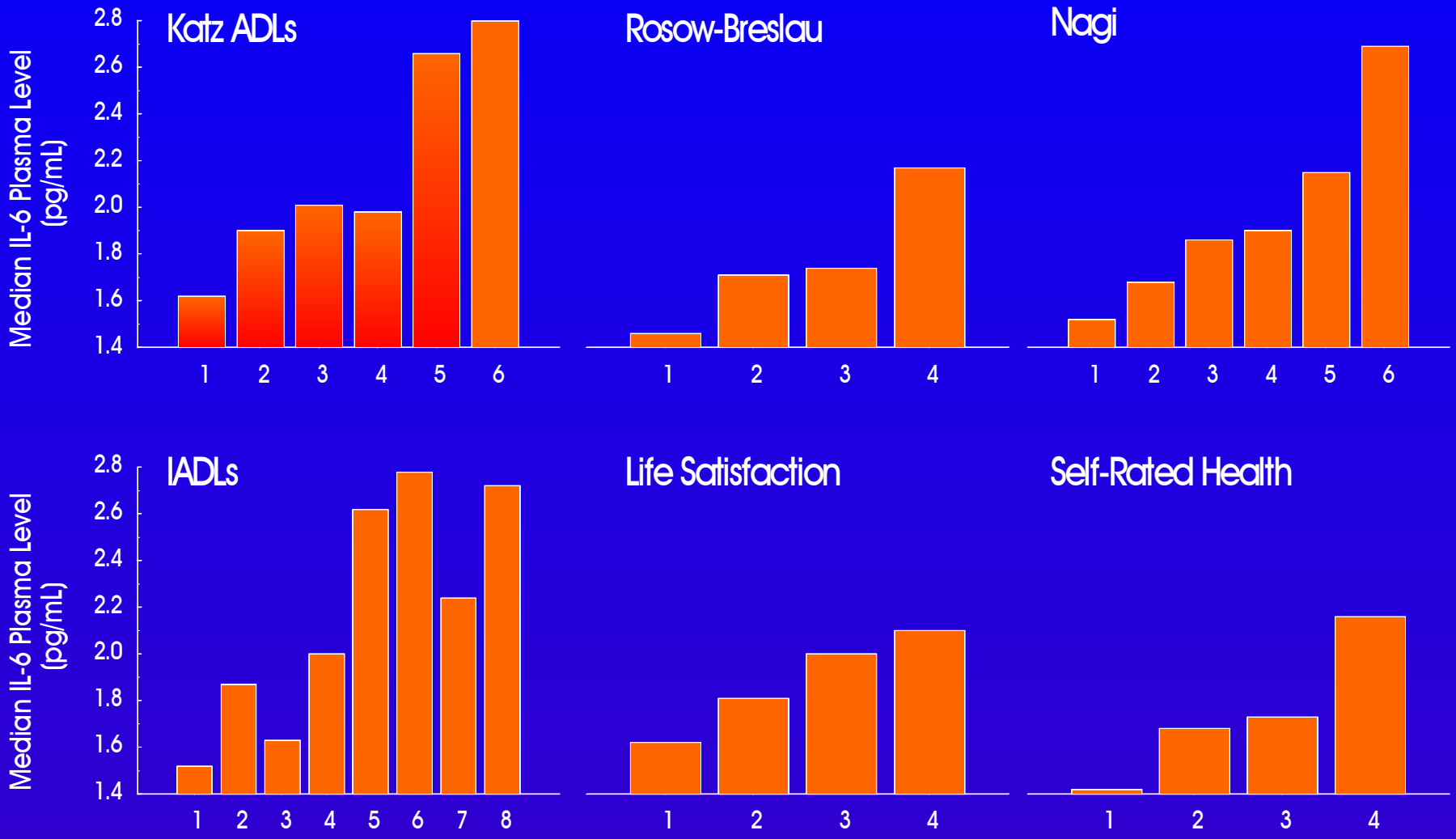
VS

"If you've seen one old person, you've seen one old person"


Life course
Genes
Environment
Personal habits
Smoking
Alcohol
Exercise
SUCCESSFUL
USUAL
FRAIL
Outcomes
Co-morbid diseases
Lots of drugs!
Disability
Death

Median IL-6 Level According to Functional Status in the Duke EPESE

(Cohen HJ et. al. The association of plasma IL-6 level with functional disability in community-dwelling elderly. Journals of Gerontology 1997; 52:M201-M208)



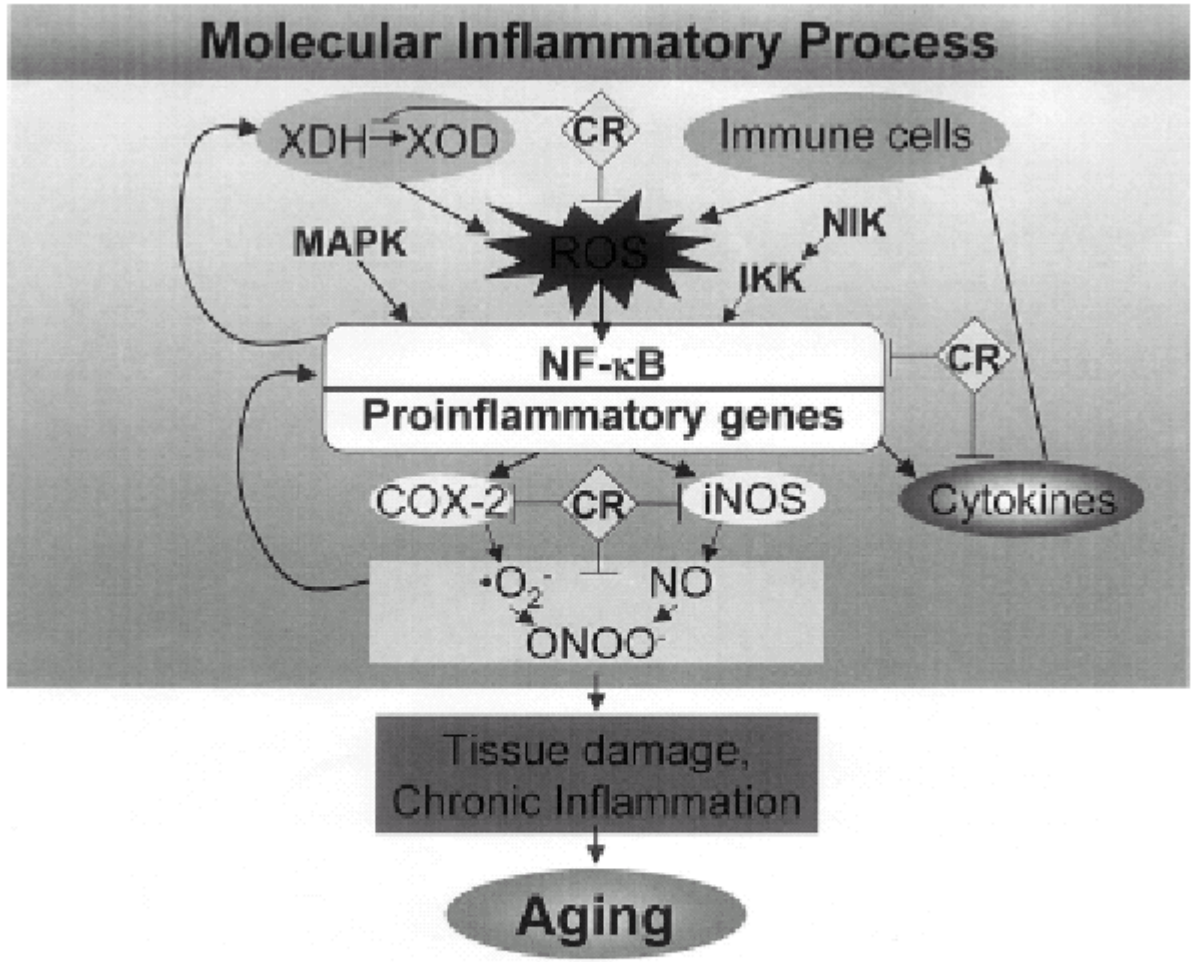


Fig. 1. Molecular inflammation hypothesis of aging based on the anti-aging mechanism of CR. XDH, xanthine dehydrogenase; XOD, xanthine oxidase; ROS, reactive oxygen species; COX-2, cyclooxygenase-2; iNOS, inducible NO synthase; $ONOO^-$, peroxynitrite; CR, calorie restriction.

IL-6 is a hallmark of inflammation

Acute inflammation

- Acute insult triggers molecular defenses including
  High pro-inflammatory cytokines from macrophages and other cells
  Acute phase activation - liver protein profile
- Constitutional symptoms
- Vital for health - resolution, death or chronic

Chronic inflammation

- Milder form
- Unresolved but controlled
- Asymptomatic
- Health benefits/detriments under investigation
  Role in wasting/sarcopenia?
  Paradoxical risk factors
  Novel risk factor disease/disabilty

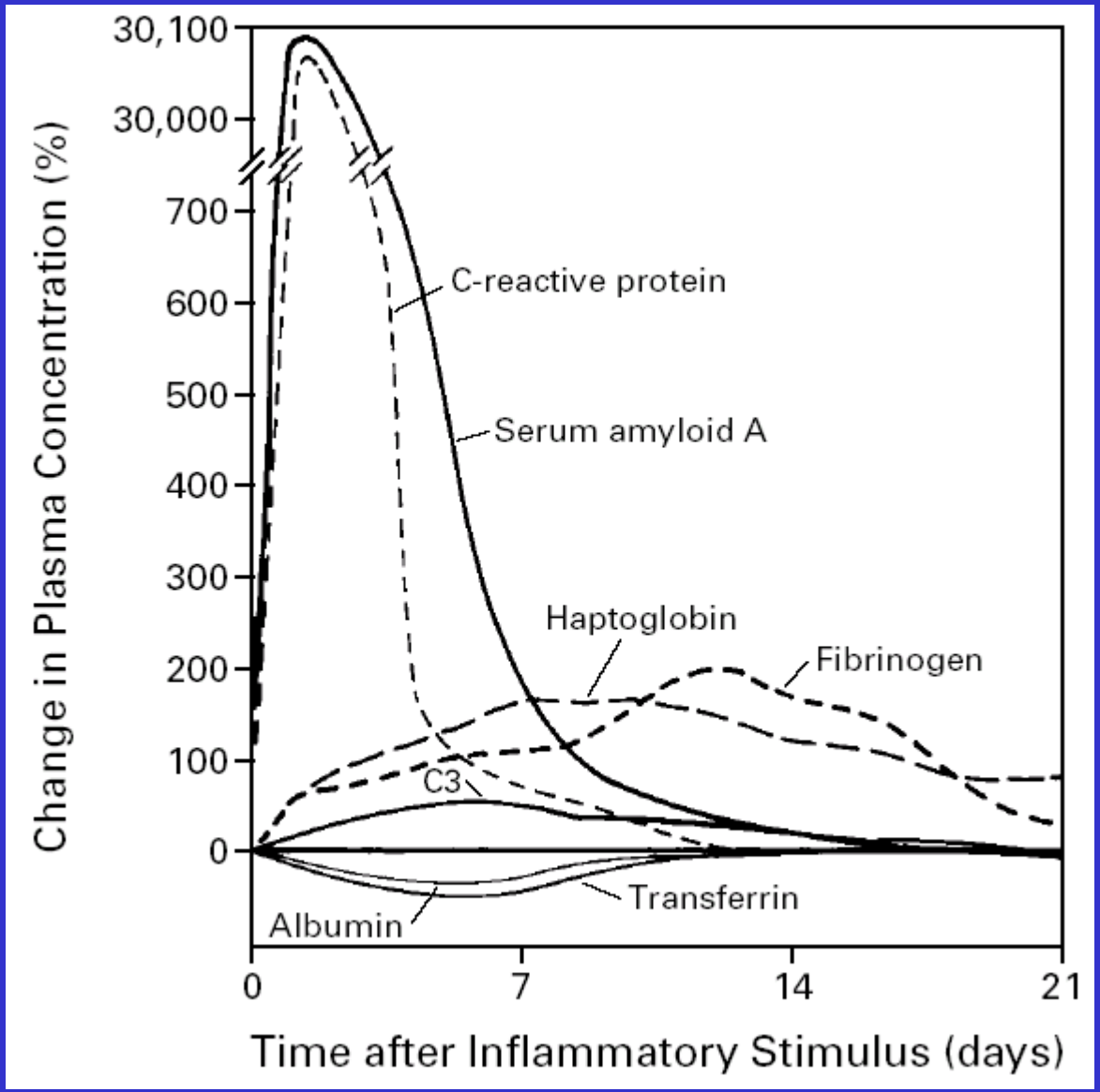

30,100
30,000
700
600
500
400
300
200
100
0
Change in Plasma Concentration (%)
C-reactive protein
Serum amyloid A
Haptoglobin
Fibrinogen
C3
Transferrin
Albumin
0
7
14
21
Time after Inflammatory Stimulus (days)

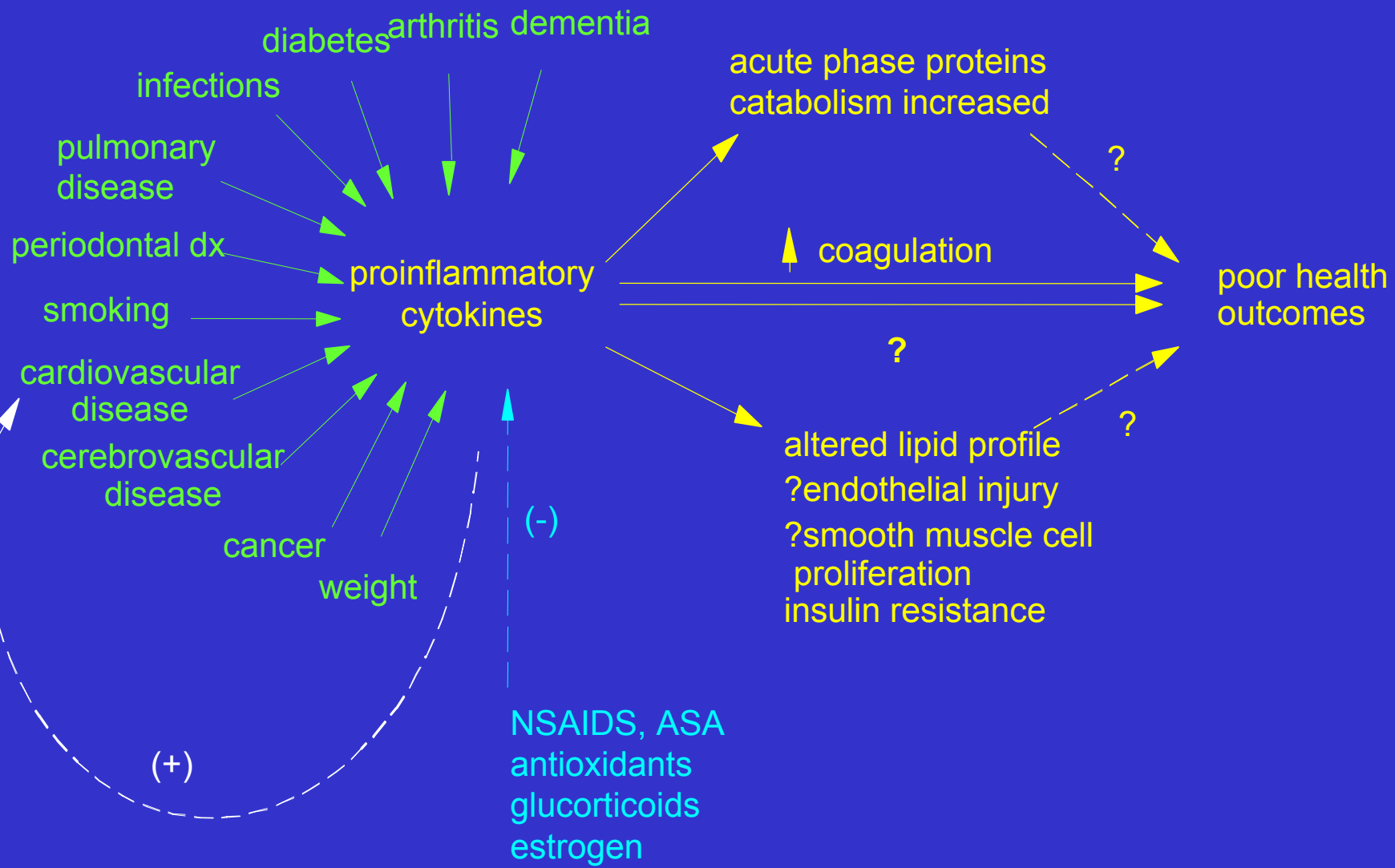
Table 3
Inflammatory and immuno-stimulating agents that induce CYP isoforms

Immunoactive agent	CYP isoform
Hepatitis B or C infection	CYP2A6
Helibacter hepaticus infection	CYP1A2, CYP2A5
Schistosoma mansoni infection	CYP1A
Trematode infection	CYP2A5
Opisthorchiasis viverrini infection	CYP2A6
LPS	CYP4F16 (renal)
IL-1β	CYP3A1
Particulate irritants	CYP4A

Table 2
Inflammatory and immuno-stimulating agents that depress CYP-dependent drug biotransformation

Trypan blue	Zymosan
Dextran sulphate	Latex breads
Turpentine	Carrageenan
Adjuvants	$BaSO_4$ particulate
Particulate irritants	Vaccines
IFN inducers	PolyrI.polyrC
IFN-α, -β, and -γ	IL-1α, -1β, -2, and -6
TGF-β	TNF-α
Escherichia coli LPS	*Corynobacterium parvum*
Staphylococcal enterotoxin B	*Staphylococcal aureus* protein A
Klebsiella pneumoniae endotoxin	*Bordetella pertussis* toxin

Inflammation and Health Outcomes in Old Age



Research needs:

Studies of pharmacologic properties of new supplements

Emphasis on heterogeneity in older population, particularly on defining risks for frail

Study effects of age-associated conditions affecting liver including fatty liver disease and inflammation

Drug interactions with multiple co-medications

Better education programs for providers and patients to communicate the results of this research

Continue search for effective supplements…..