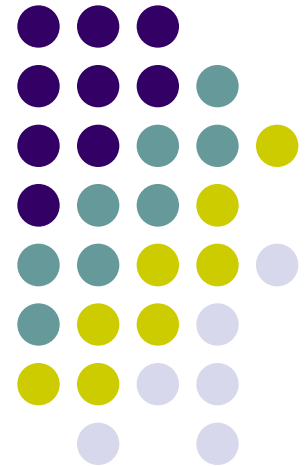


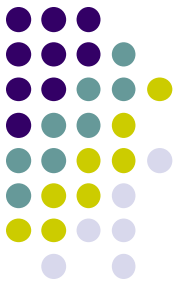
UAB and Geriatrics

Tomas L. Griebling, MD, MPH

**John P. Wolf 33° Masonic Distinguished
Professor of Urology**

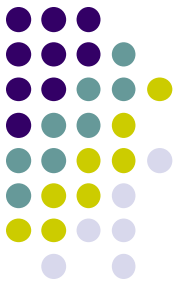
**Department of Urology and
The Landon Center on Aging
The University of Kansas**





Educational Objectives

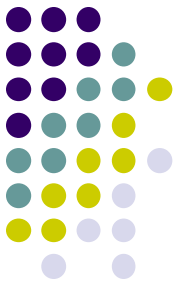
- Discuss demographics / epidemiology of aging
- Describe theoretical concepts of aging
 - Senescence
 - Ischemia, oxidative stress, reperfusion injury
- Review translational and clinical research on ischemia and bladder dysfunction in older adults
- Consider the progression model of LUTD
- Link to other geriatric syndromes
- Discuss future implications



Definitions

- Geriatrics
 - Age 65+ years (USA definition)
 - Medicare
 - Social Security
 - WHO definition = 60+ years
 - New definitions = 75+ years

Demographic Imperatives

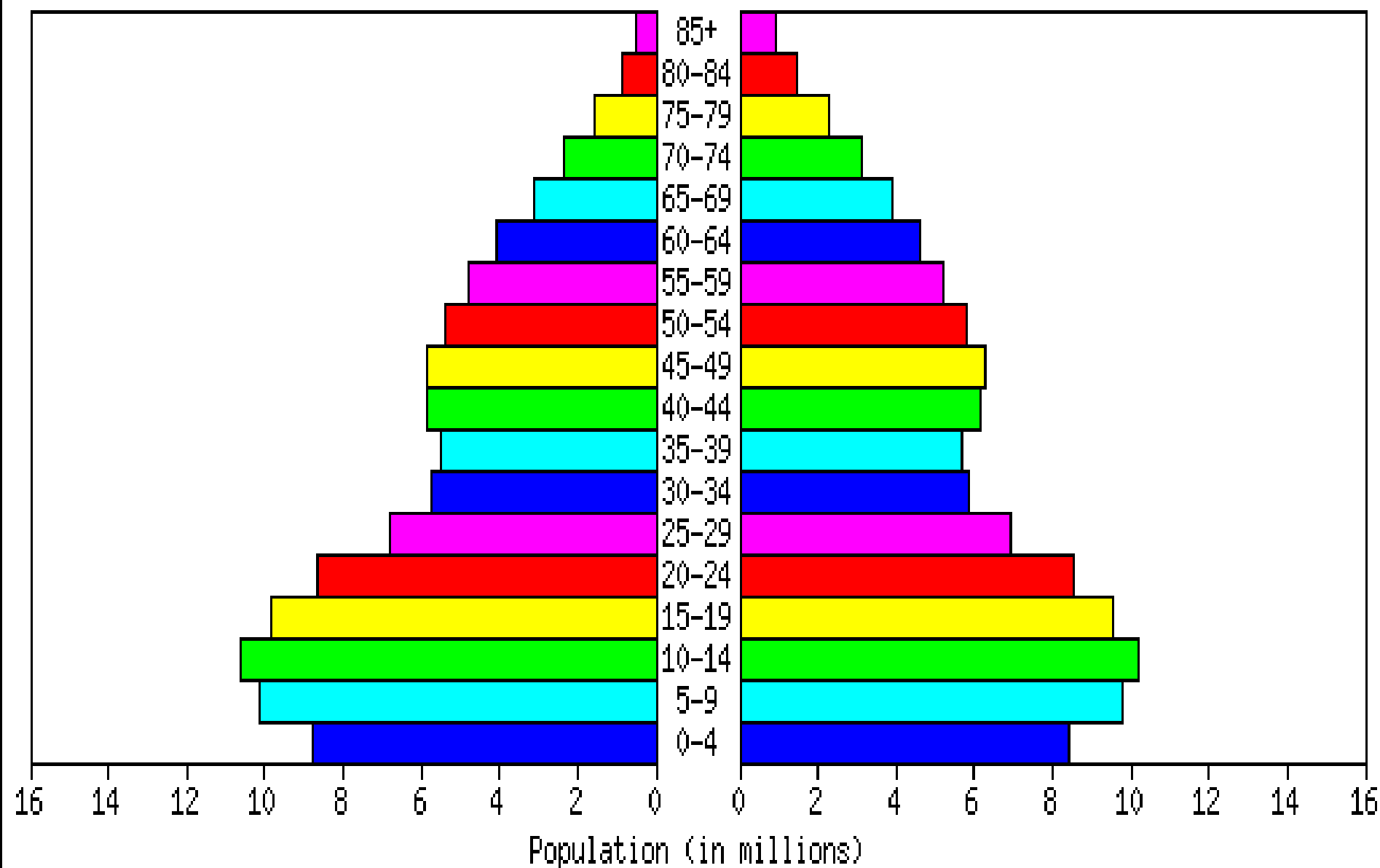


- Elderly (> 65 years) currently comprise 13% of the total USA population
- Predicted to reach 20%+ by 2030
- Baby boom generation is aging
 - 10,000 people / day turn 65+ in the USA
- Worldwide phenomenon
- Fastest growing segment > 85 years

United States: 1970

MALE

FEMALE

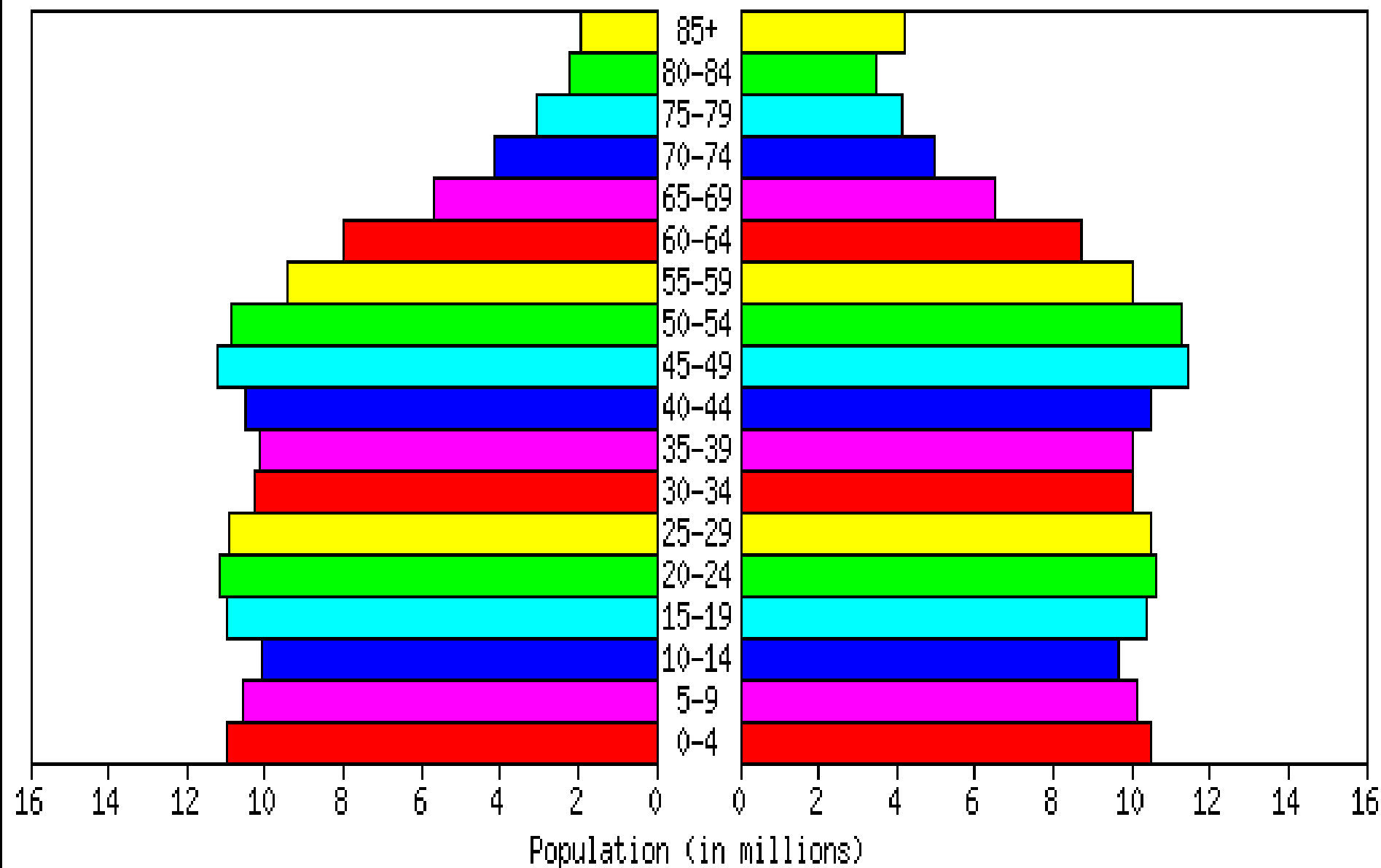


Source: U.S. Census Bureau, International Data Base.

United States: 2010

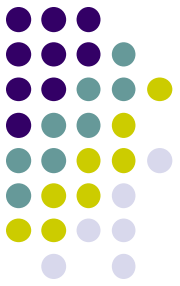
MALE

FEMALE



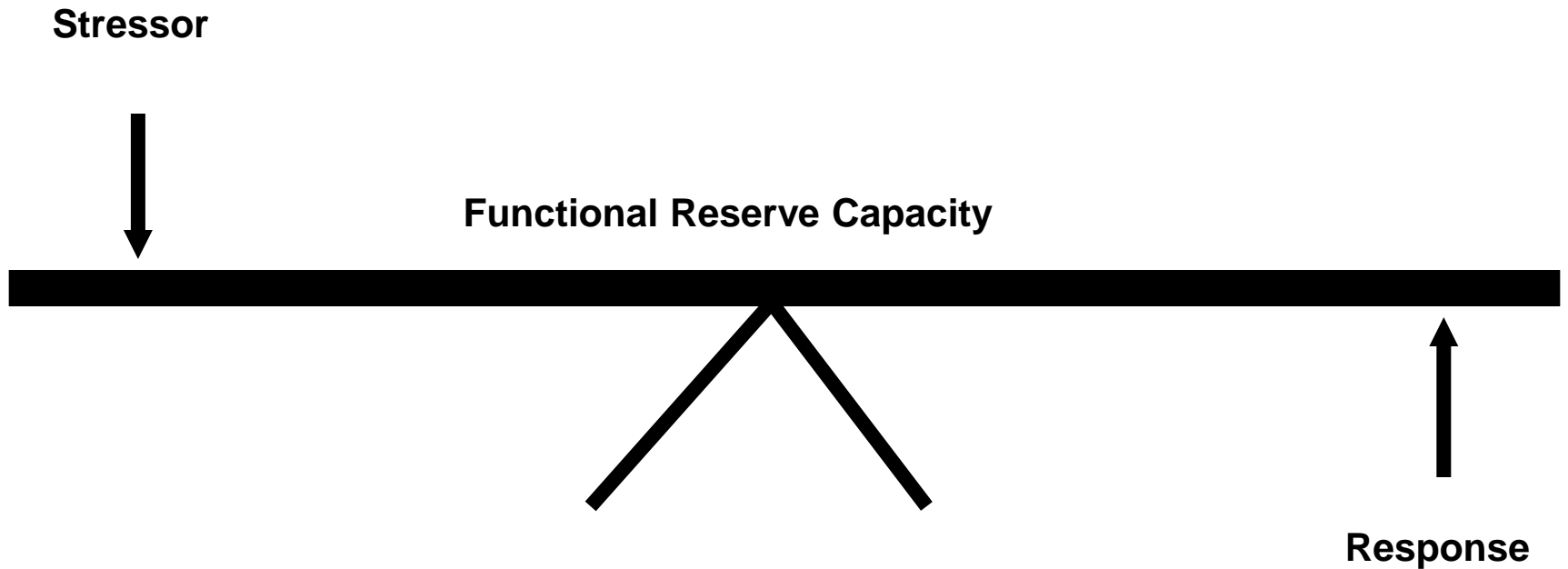
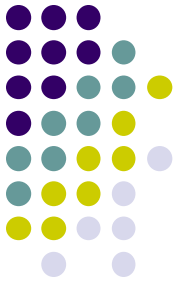
Source: U.S. Census Bureau, International Data Base.

Demographic Imperatives

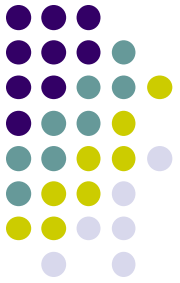


- Worldwide phenomenon
- Population ≥ 65 years old
 - 1999 410 million
 - 2000 420 million
 - 2030 (estimate) 973 million
 - 71% (690 million) in developing countries

Homeostasis



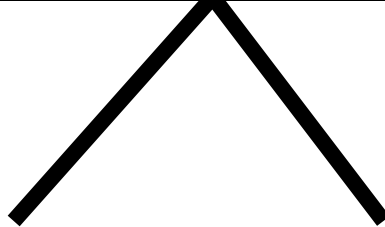
‘Homostenosis’



Stressor

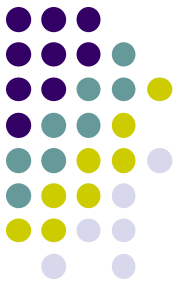


Functional Reserve Capacity

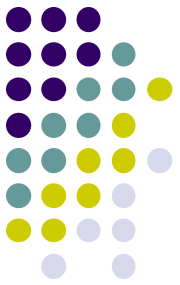


Response

Senescence

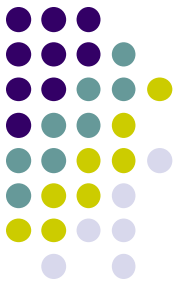


Senescence



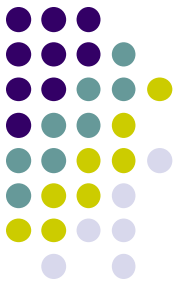
- *In vivo* – cellular / tissue / organ / organism
 - Hayflick principle
 - Limited number of cell divisions
 - Cell culture studies
 - Telomere shortening
 - Oxidative stress with free radical formation
 - DNA methylation
 - Apoptosis – programmed cell death

Senescence



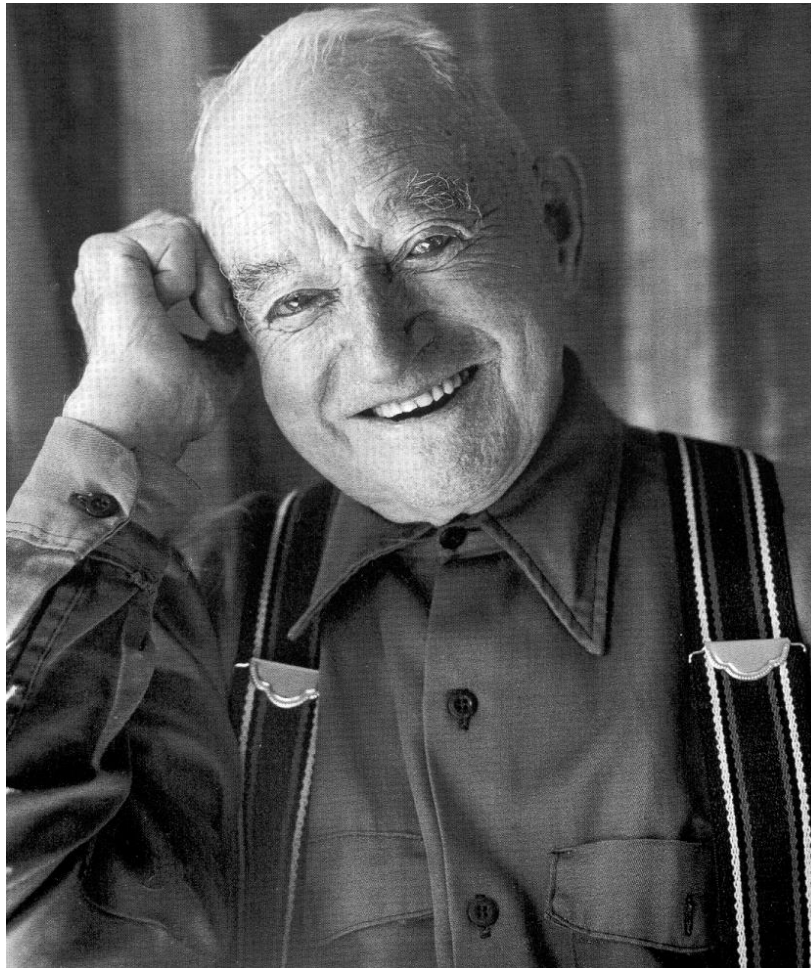
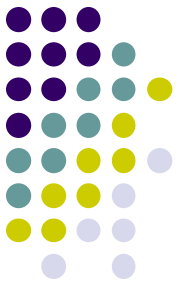
- Allergic, irritant, and inflammatory responses all blunted in aging
- May compromise wound repair function in elderly patients
- Role of inflammation controversial
 - Acute inflammation – protective?
 - Chronic inflammation – harmful?

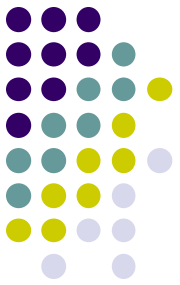
Senescence



- Decreased number of cell divisions needed for granulation tissue formation
- Increased deposition of cross-linked collagen
 - Diminished tissue elasticity
 - ? Alters wound healing
- Increased mitogen activated protein (MAP) kinases and other entities
- Changes in tissue vasculature
 - Large and small vessel changes

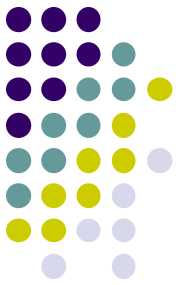
Ischemic Disease





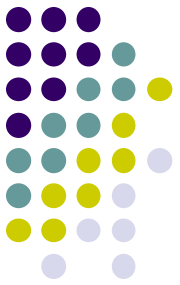
Epidemiology

- Ischemic diseases are common in older adults
 - Cardiovascular disease
 - Atherosclerosis
 - Diabetes
 - Metabolic syndrome
 - Erectile dysfunction
 - Smoking
- Role of vascular integrity has been shown in multiple organ-systems and conditions



Animal Models of Ischemia

- Diabetes models
 - Vascular injury models
 - Outlet obstruction models
 - Aging models
-
- Each has advantages and disadvantages
 - Depends on mechanism of interest



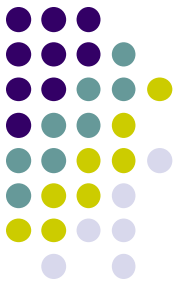
Ultrastructural Changes

- Classic studies on bladder anatomy
- Cellular disruption
- Mitochondrial damage
- Reduction in smooth muscle and increase in collagen and connective tissue
- Correlates to urodynamic and clinical signs and symptoms

Elbadawi A, et al: J Urol 1997; 157: 1814-1822

Elbadawi A, et al: J Urol 1998; 157: 1802-1813

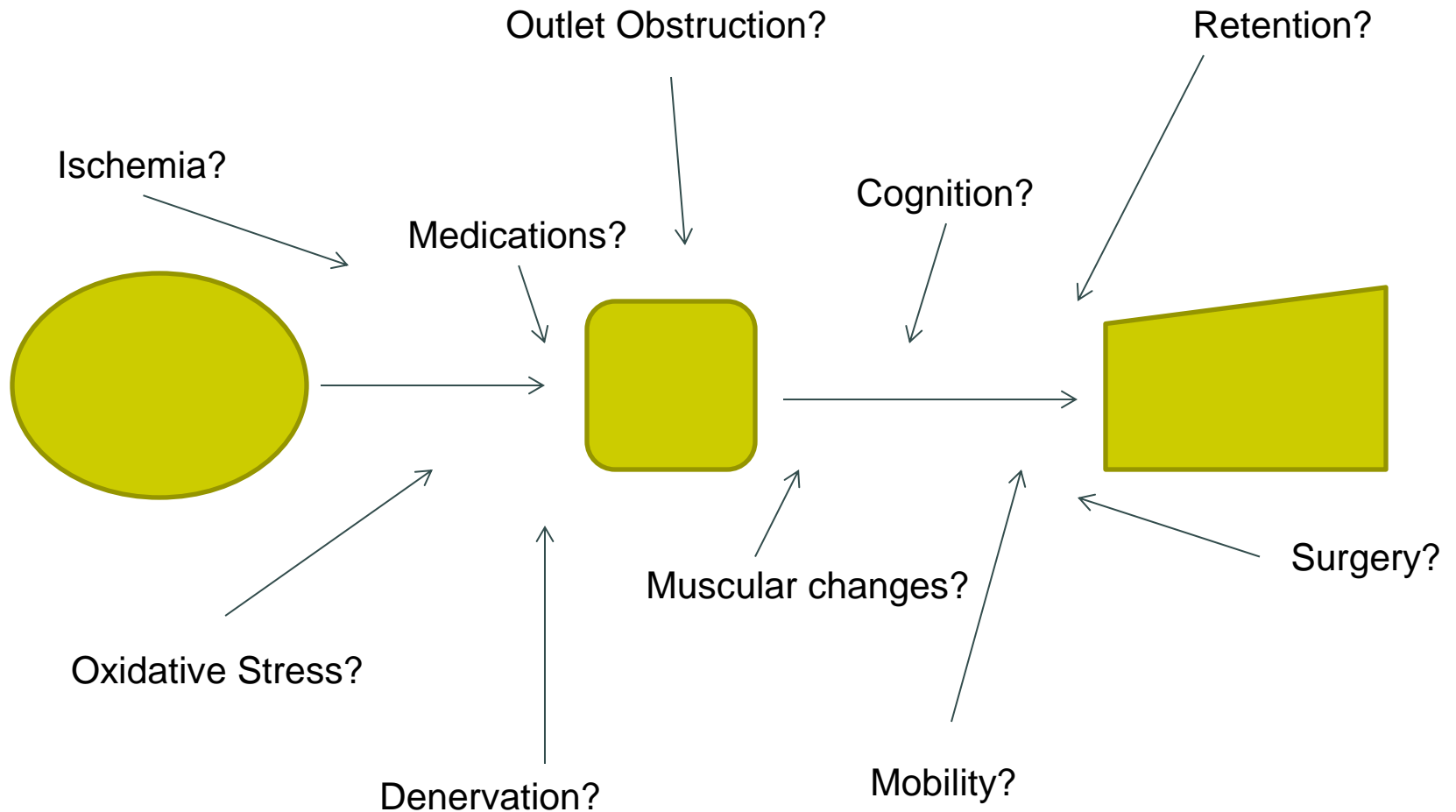
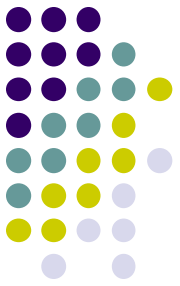
Brierly RD et al: J Urol 2003; 169: 1374-1378



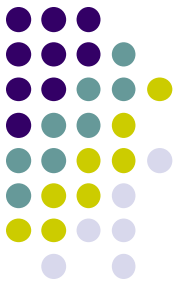
Progression Model of LUTD

- Range of symptoms may overlap
 - Urinary urgency, frequency, urge incontinence
 - Obstructed voiding symptoms
 - Other urinary incontinence
 - Incomplete emptying (? Overflow)
- Bladder overactivity may be an early sign
- Repetitive ischemia and reperfusion injury
- Ultrastructural changes and neurodegeneration
- Progression to underactive bladder

Progression Model



Bladder Ischemia – Translational Research

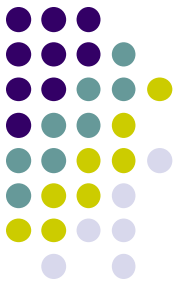


- Atherosclerotic injury
 - Increase oxidative stress markers and proinflammatory cytokines (IL-6, IL-8, TNF- α)
 - Downstream atherosclerotic changes in small vessels in bladder
 - Decreased bladder contractile response
 - Increased collagen to muscle ratio in bladder
 - Reduction in tissue innervation to bladder

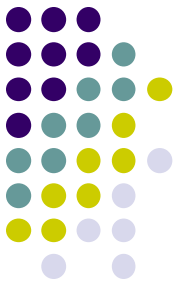
Nomiya M, et al: Neurourol Urodynam 2012; 31: 195-200

Sagawa K, et al: Urology 2013; 81: 1379.e9-1379.e14

Clinical Correlates

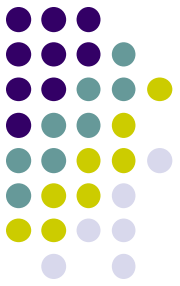


Bladder Ischemia – Clinical Research



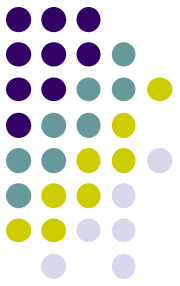
- In-vitro studies with human cells show importance of adequate oxygen tension
 - Cellular antioxidant function decreased with oxidative stress (ischemia / reperfusion)
 - Unchanged in chronic hypoxia
 - Raises question if repetitive vascular injury and reperfusion could lead to organ dysfunction
 - Chronic bladder overdistension
 - Progression model of bladder function

Bladder Ischemia – Clinical Research



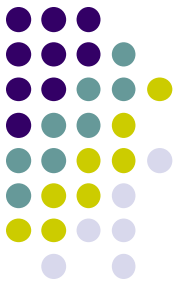
- Chronic ischemia associated with both BPH and erectile dysfunction
 - TRUS with Color-Doppler
 - Men with BPH, DM and controls
 - Decreased perfusion of transition zone (high RI) in both BPH and DM compared to controls
 - Correlation between vascular change and worse IPSS
 - More pronounced for men with atherosclerotic disease
 - Associations with erectile dysfunction also noted

Bladder Ischemia – Clinical Research



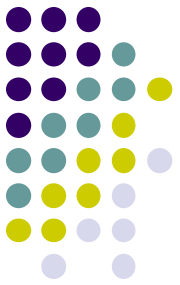
- Bladder vascular resistance
- Color-Doppler ultrasonography
- 10 subjects and 10 controls
 - Higher resistive index correlates to BOO symptoms
 - Greater severity of BOO associated with higher RI compared to mild, moderate symptoms or controls
 - TURP with relief of obstruction led to improved RI
 - ? Persistent urgency due to continued ischemia

Bladder Ischemia – Clinical Research

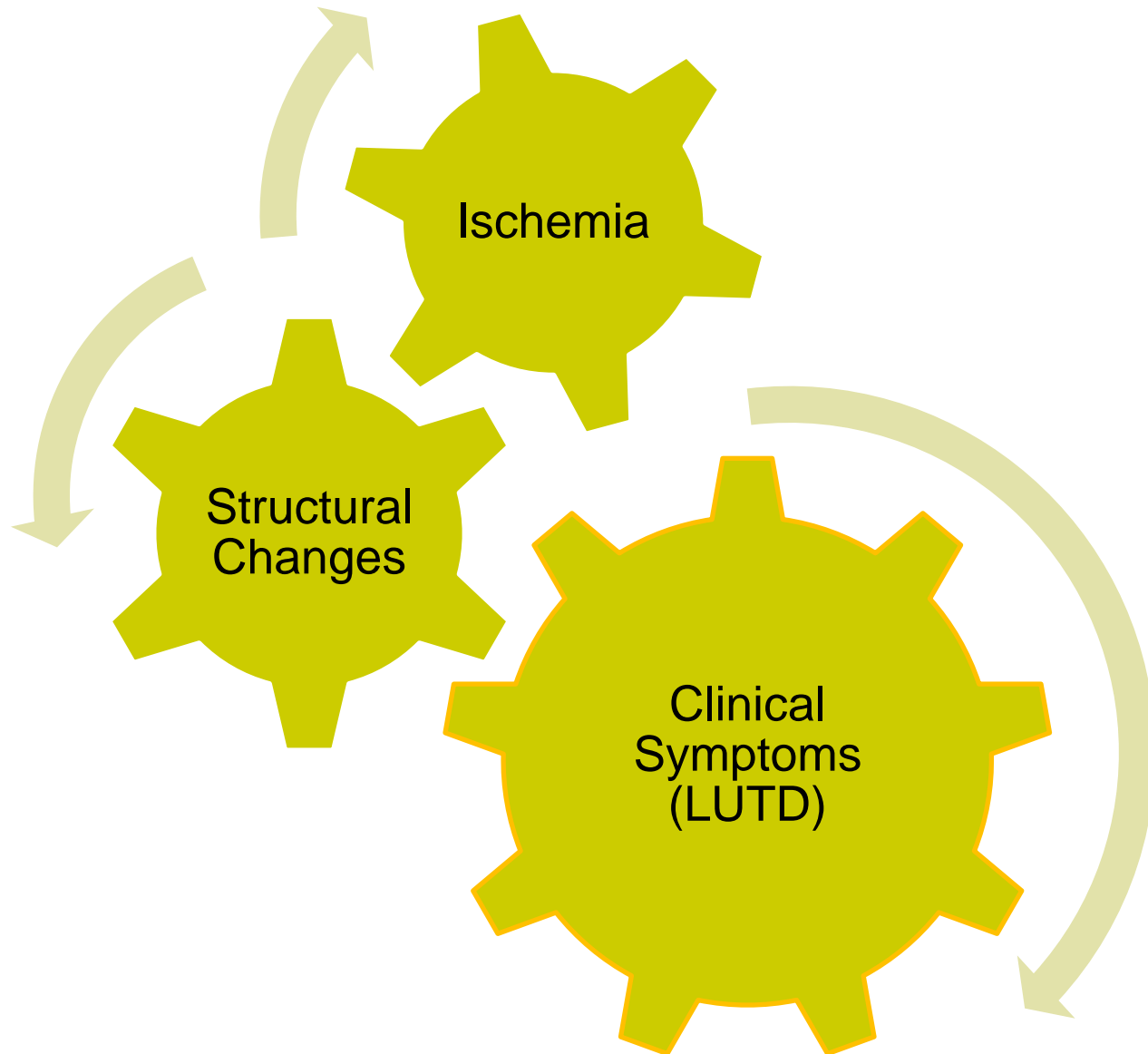
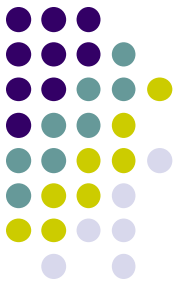


- Lower extremity and pelvic ultrasound
 - Color-Doppler
 - 32 older adults and 20 controls
 - 12 women (82.3 years); 10 women (42.3 year)
 - 20 men (79.4 years); 10 men (41.5 years)
 - Resistive index (RI) worse in older adults with LUTS
 - Urinary frequency and nocturia strongly negatively correlated with vascular perfusion

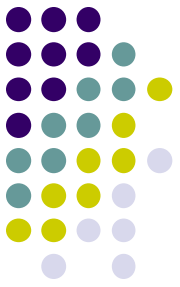
Bladder Ischemia – Clinical Research

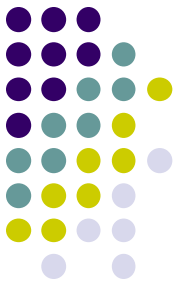


- Role of changes in ischemia with treatment
 - Alpha-blocker therapy for BOO
 - 19 men with BOO/LUTS and 4 controls
 - Color-Doppler ultrasound and urodynamics
 - Comparison pre- and post-treatment
 - All men with BOO/LUTS had decreased arterial flow and increased vascular RI
 - Alpha-blocker significant improved vascular function and decreased RI (132.8%), and urodynamic parameters



Functional Issues in Geriatrics

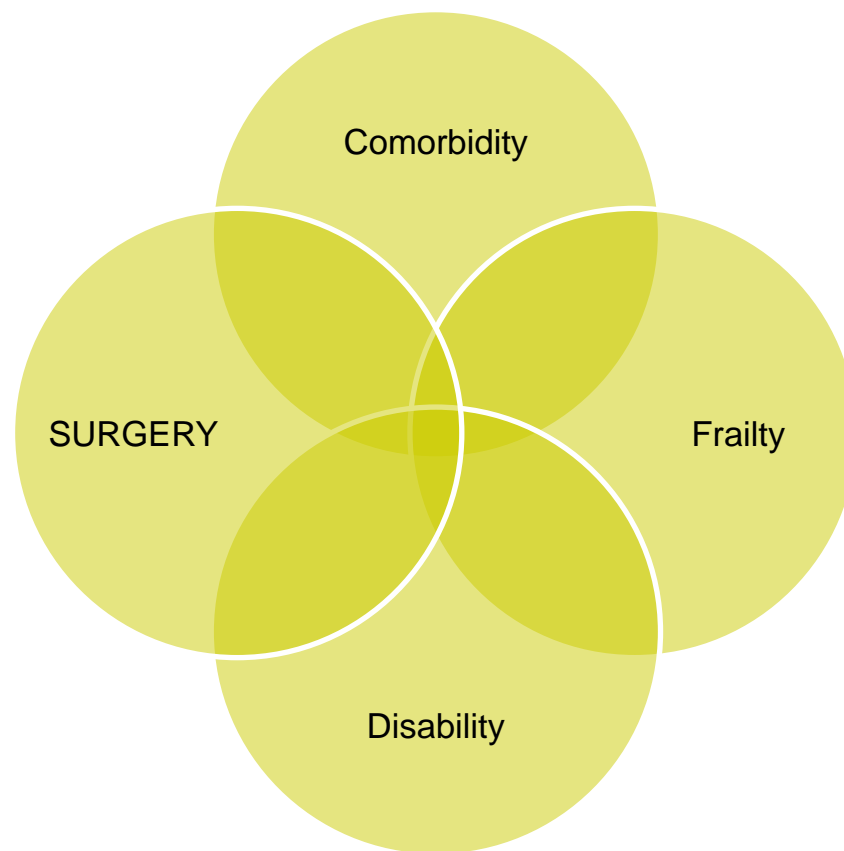


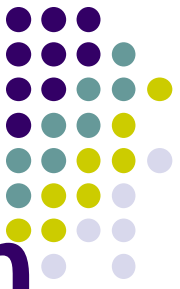


Functional Assessment

- Activities of Daily Living (ADLs)
 - Bathing, grooming, eating, dressing, ambulation or other mobility, and toileting
- Instrumental Activities of Daily Living (IADLs)
 - Shopping, housekeeping, laundry, using telephone, taking transportation, balancing finances, preparing food or medications
- Provides insight into level of independence or dependence and may predict some outcomes

Risk Assessment

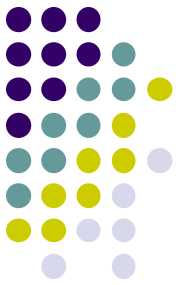




Predictive Value of Function

Functional Status at Age 70	Average Life Expectancy (years)	Annual Health Care Costs (\$)
Independent	14.3	\$4600
IADL Deficit Only	12.4	\$8500
1+ ADL Deficit	11.6	\$14,000

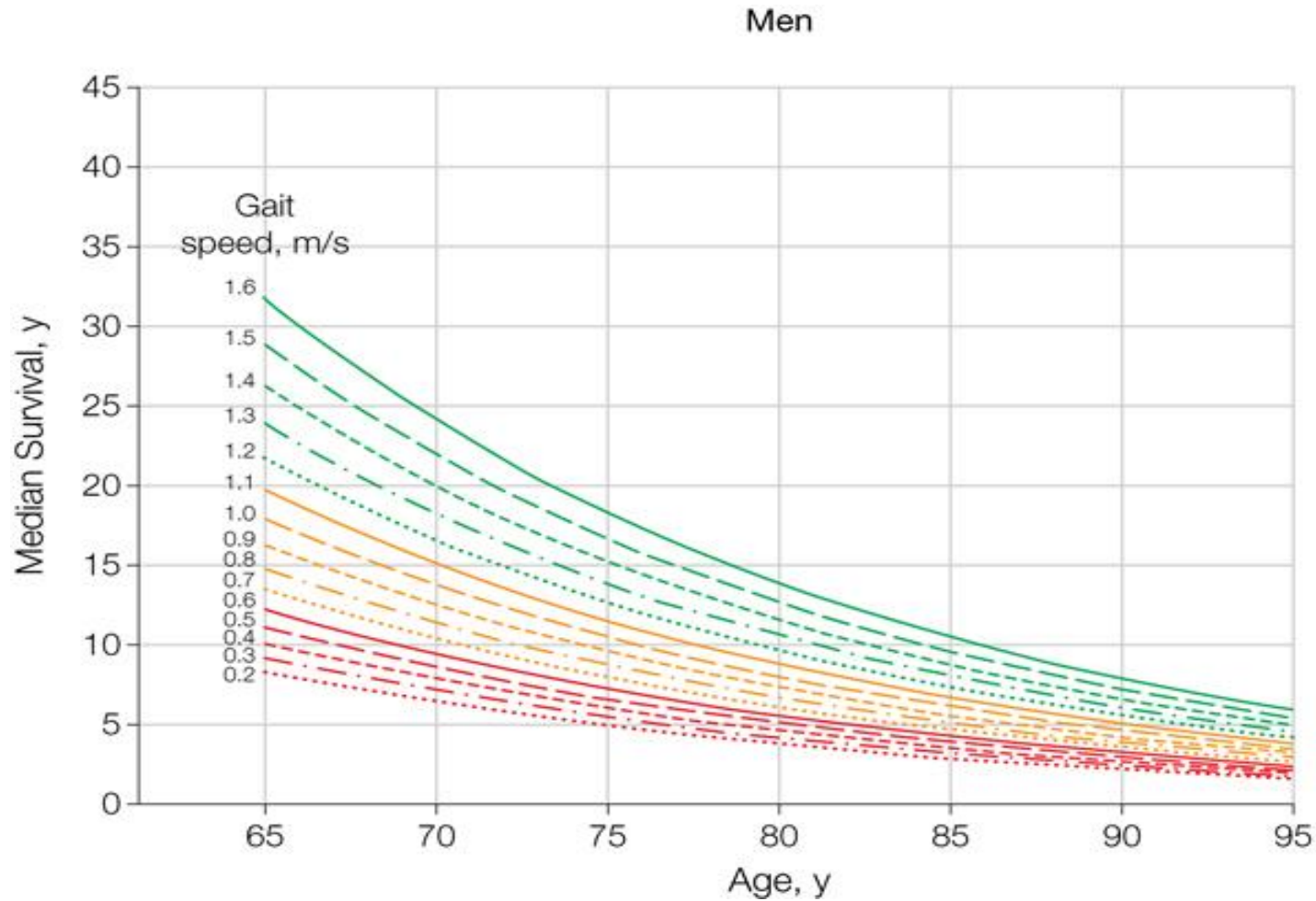
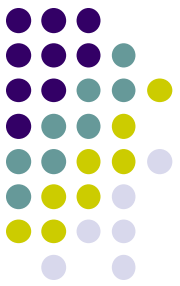
Lubitz et al *NEJM* 349:1048-1055, 2003



Mobility Assessment

- Important for independent toileting
- 'Get Up and Go Test'
 - Stand from chair, walk 3 meters, turn, return and sit down
 - Allowed to use mobility assistive devices (walker, cane)
 - Measures quadriceps strength, mobility, gait, balance, transfers, and ability to follow instructions
 - Timed vs. untimed
 - ≤ 10 seconds – most adults
 - 11-20 seconds – normal for frail older adults

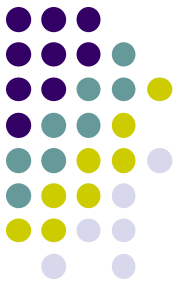
Median Life Expectancy for Men Gait Speed



Studenski, S. et al. JAMA 2011;305:50-58

JAMA

Cognitive Assessment

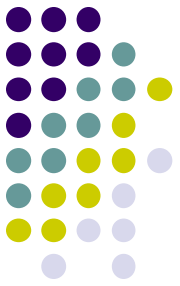


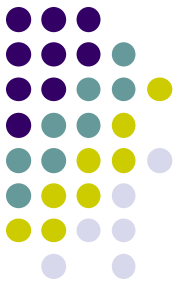
- Cognitive Assessment
 - Important in overall assessment of older adults
 - Informed consent and decision-making capacity
 - Some treatments may influence cognition (medications)
 - Folstein Mini-Mental State Exam (MMSE)
 - 13 items – 30 points
 - Mini-Cog
 - 3 item recall and clock-drawing test

Folstein MF, et al: J Psychiatr Res 1975, 12: 189-198

Borson S, et al: Int J Geriatr Psychiatry 2000, 15: 1021-1027

Geriatric Syndromes

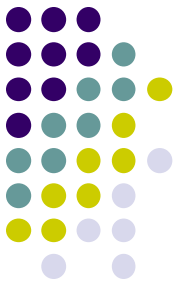




Delirium

- Multifactorial syndrome
- High incidence after surgery
 - 10-15% of elective non-cardiac surgery
 - > 50% after emergency surgery
- Increased risk mortality within one year (2-3x)
- Increased risk cognitive decline, nursing home
- Beware underlying risks (prior episode, dementia)

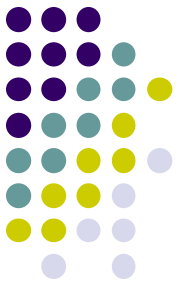
Arch Intern Med 162:457-463, 2002
JAMA 291: 1753-1762, 2004



Polypharmacy

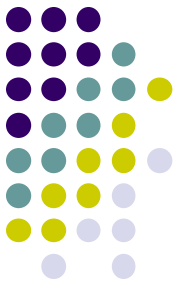
- 13% population / consume 37% medications
- Alterations in metabolism with aging
- Overall 7x increase in side effect profiles
- Overall 2-3 x increase adverse drug reactions
- Exponential ADR increase with number
 - 2 drugs = 15%; 5 drugs = 50-60%
- Avoid the 'Prescribing Cascade' – new Rx to treat side effects of other drugs

Frailty

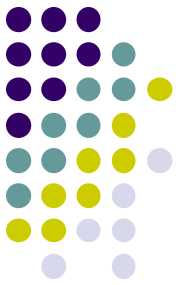


- Syndrome of changes associated with increased impairment in elderly patients
 - Decreased walk time / gait speed
 - Diminished grip strength
 - Decreased physical activity levels
 - Exhaustion
 - Weight loss (> 10 pounds or 5% total weight)

Frailty



- Increased levels of inflammation associated with frailty (biomarkers)
- Women's Health & Aging Study
 - 558 women
 - WBC and IL-6 independently associated with frailty
 - Top tertile WBC: OR 3.15 (95% CI = 1.34 – 7.41)
 - Top tertile IL-6: OR 2.81 (95% CI = 1.19 – 6.64)
 - Combined: OR **9.85** (95% CI = 3.04 – 31.99)

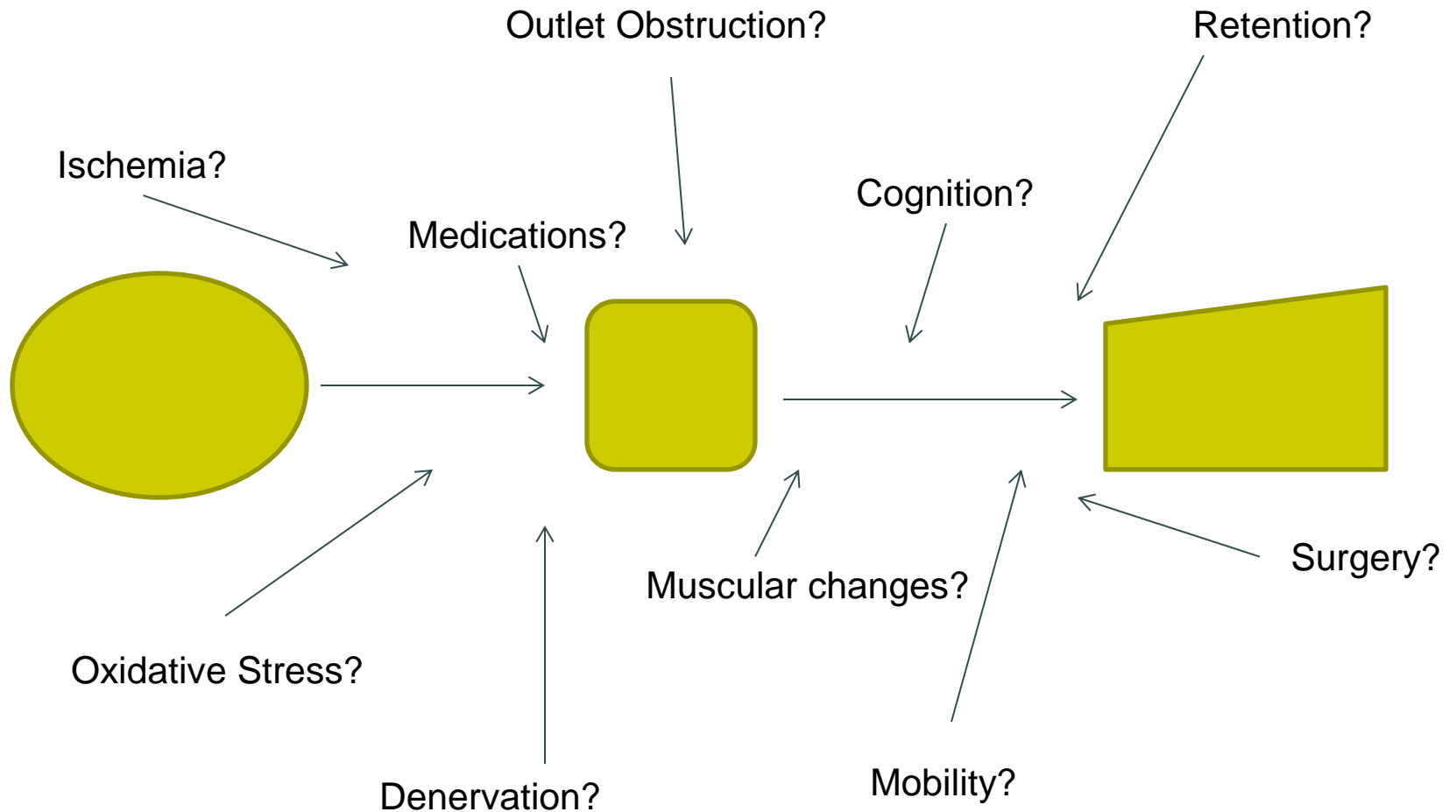
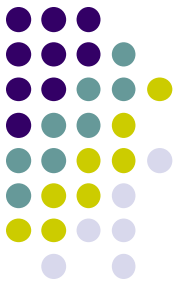


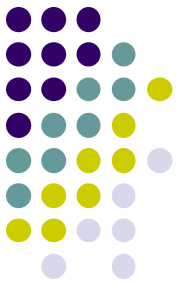
Frailty and surgery

- N = 594 patients
- Age > 65 years
- Independently predicts surgical outcomes
 - Complications: OR (2.06 / 2.54)
 - LOS: OR (1.49 / 1.69)
 - Discharge status: OR (3.16 / 20.48)

Makary et al, J Am Coll Surg 210: 2010

Progression Model





Summary

- Rapidly aging population
- Links between comorbidities and UAB
- Ischemia / reperfusion
 - Role of chronic obstruction
 - Progression model
- Ultrastructural and organ-system changes
- Geriatric syndromes
- Potential target for therapy





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