

Frailty and Inflammation as Markers of Late Life Vulnerability

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Frailty

- A geriatric syndrome of weakness, weight loss, and low activity associated with adverse health outcomes
- An age-related, biological vulnerability to adverse outcomes that stems from alterations in multiple physiological systems

A Clinical and Research Tool

■ In clinical practice

- to identify those at highest risk for adverse clinical outcomes
- to develop interventions to decrease risk

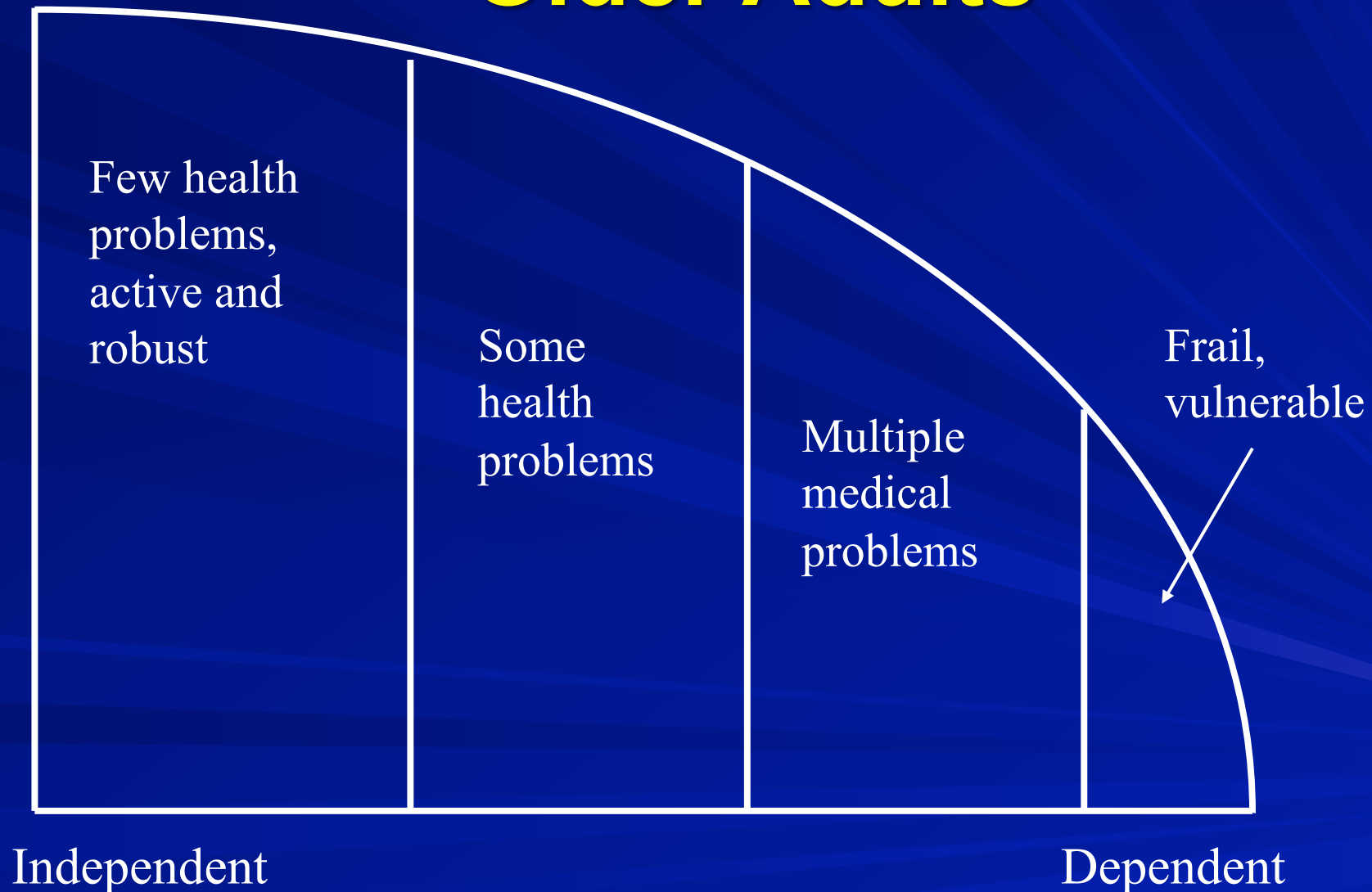
■ As a research tool

- to study the biological etiologies of late life decline and age-related chronic diseases
- to study age-related, multisystem decline

Why Does Frailty Matter?

- Highest risk for poor outcomes
- Slowest recovery rate
- Most iatrogenic complications
- Highest mortality rate
- Key to understanding late life decline

Heterogeneity in Health of Older Adults



Clinical Case 1:

75 yo male, admitted for elective total knee replacement

PMHx: CHF, HTN, knee OA

Functionality: lifts weights, walked 2 miles a day until knee pain worsened

Clinical Case 1:

- Surgery was without complications
- Returned home on PO Day 3 on narcotics for pain and anticoagulation
- Received outpatient PT for 2 weeks

Clinical Case 2:

75 yo male, admitted for elective total knee replacement

PMHx: CHF, HTN, knee OA

Functionality: Volunteers regularly, less so in past months secondary to fatigue, knee pain

Clinical Case 2:

- No problems in OR
- Developed delirium on low dose narcotics in PO Day 1
- Fell getting out of bed
- Developed incontinence
- Refused all PT/OT interventions

Clinical Case 2:

- Transferred to sub-acute rehab on PO Day 5
- Improved slowly over 2 weeks
- Discharged to home 18 days after operation
- Received home PT for 2 more weeks and was at baseline 3 months later

Clinical Case 3:

82 yo male with non-syncopal fall,
couldn't get up off floor secondary to
weakness

PMHx: HTN, OA hips & hands, femoral
neck fracture 3 years prior, 15 lb
weight loss since that fracture

Functionality: lived alone, performs all
ADLs and IADLs, walks in house and
to mailbox

Clinical Case 3:

- Cachetic and weak
- Medical work-up completely negative
- No evidence of major depression

Clinical Case 3:

- Transferred to sub-acute rehab facility
- Ambulated 30 ft with walker after 2 weeks
- Unable to care for self; transferred to assisted living facility
- Dies suddenly 3 months later, probable cardiovascular etiology

The Beginning: Clinical Observations by Clinicians

- Shrinking, weight loss, low activity correlated with vulnerability to getting sick and dying
- Frail, older adults often resemble other patients with malignancy or inflammatory diseases

Frailty Phenotype Development

- Weight loss
- Weakness
- Exhaustion
- Slowed walking speed
- Low activity

* Frail if 3 of 5 are present

Frailty Status Predicts Adverse Outcomes

	CHS	WHAS
Incident Fall	1.29 (1.00 – 1.68)	1.18 (0.63, 2.19) (NS)
Worsening Mobility	1.50 (1.23, 1.82)	10.44 (3.51, 31.00)
Worsening ADL Disability	1.98 (1.54 – 2.55)	15.79 (5.83, 42.78)
First Hospitalizations	1.29 (1.09,1.54)	0.67 (0.33, 1.35) (NS)
Death	2.24 (1.51,3.33)	6.03 (3.00, 12.08)

Hazard Ratios Estimated Over 3 Years, covariate adjusted, $p > 0.01$

Fried ,L. P , et al, J Ger Med Sci, 2001

Bandein-Roche et al, J Ger Med Sci, 2006

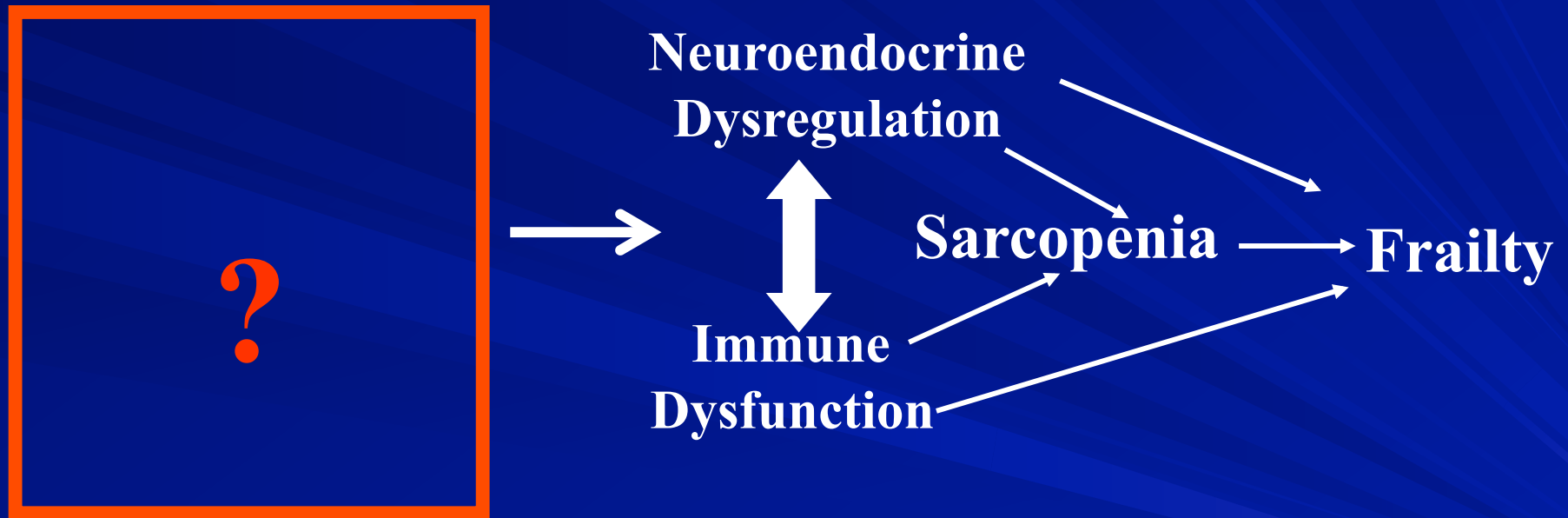
Hypothesis Development



Frailty and Failure to Thrive in Principles of Geriatric Medicine and Gerontology (Wm Hazzard, Ed.) 1998.

Pathophysiologic Hypotheses

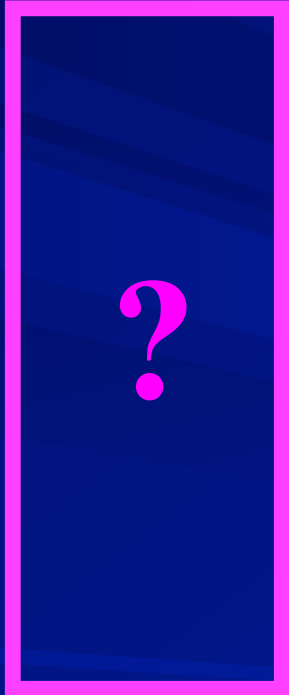
Physiology



Walston, Fried. Frailty and The Older Male. Medical Clinics of North America. 1999

Modal Pathway- 2011

Molecular & Genetic



Physiology

↑ IL-6, CRP,
WBC

↑ Clotting
process

Glucose
intolerance

↓ IGF-1,
DHEA-S

↑ **Cortisol**

Syndrome

Weakness

Weight loss

Slowed
performance

Exhaustion

Low activity

Outcomes

Falls

Disability

Dependency

Death



Fried, et al., Gerontology 2001

Walston, et al., Archives of IM 2002

Varadhan ,et al, Gerontology, 2008

Leng, et al., Aging 2004

Pathophysiologic Model for Adverse Outcomes in Older Adults

Triggers

Aging

↑ Free radicals
Senescent cells
Shortened telomeres
DNA damage

Gene Variation

Disease

Depression
Cancer
Chronic Infection
Cardiovascular disease
Diabetes/Obesity

Physiology

Activation of
Inflammation

CRP
IL-6

IL-6

DHEA-S
Cortisol

Neuroendocrine
Dysregulation

IGF-1
DHEA-S
Cortisol

Anorexia
Anemia
Sarcopenia
Osteoporosis
Hyperglycemia
↑ Clotting
↑ Mild
Cognitive
impairment

Outcomes

Frailty

Disability
Disease
Death

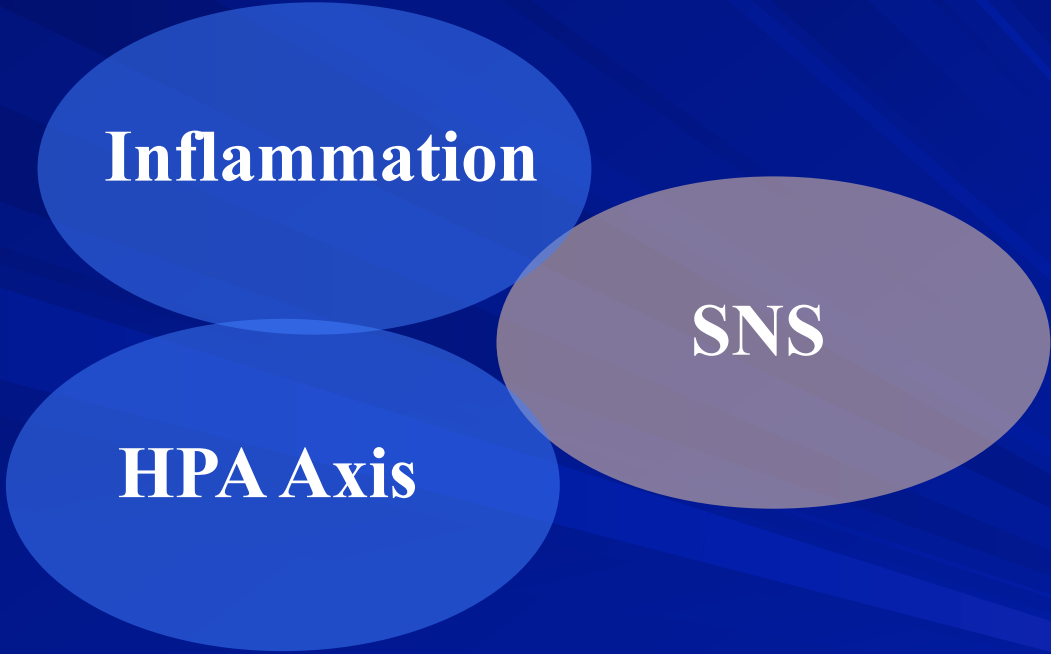
Dysregulated Biological Systems Hypothesized to Underlie Frailty

Inflammation,

SNS

HPA Axis

Dysregulated Biological Systems Hypothesized to Underlie Frailty



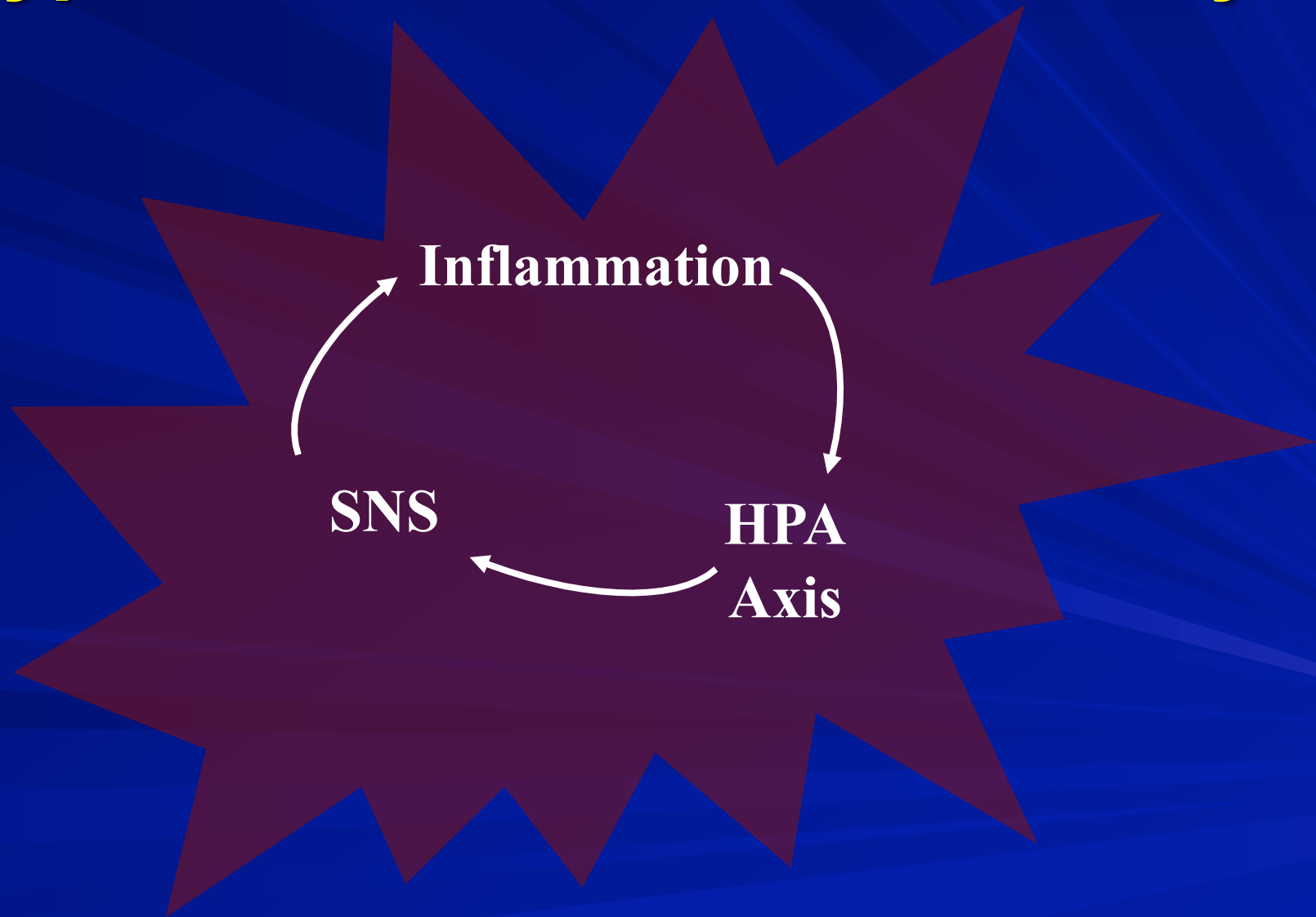
A Venn diagram consisting of three overlapping ovals. The top-left oval is labeled 'Inflammation', the bottom-left oval is labeled 'HPA Axis', and the right oval is labeled 'SNS'. The ovals are filled with shades of blue and purple, with the rightmost oval being a lighter, more translucent shade. The background is a dark blue with diagonal lines.

Inflammation

HPA Axis

SNS

Dysregulated Biological Systems Hypothesized to Underlie Frailty



Dysregulated Biological Systems Hypothesized to Underlie Frailty

Organ and tissue specific changes

Disease

Inflammation

SNS

HPA
Axis

Depression

Disability



Inflammation and Poor Health in Older Adults

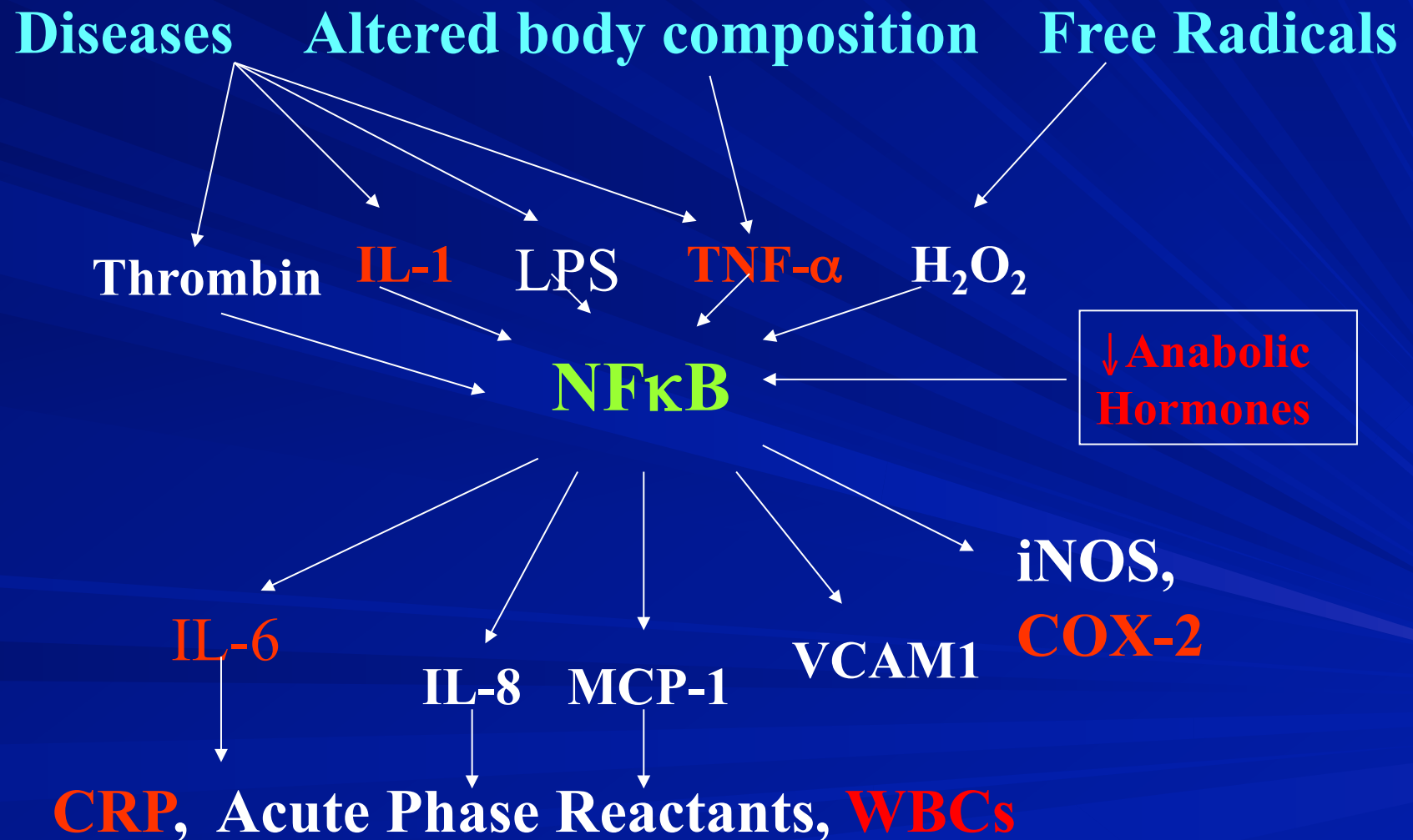
- Dozens of association studies
- Evidence for direct pathological impact of inflammatory mediators on multiple cell and tissue types
- Evidence that inflammation contributes to specific disease states

Evolving Definition of Inflammation in Geriatrics

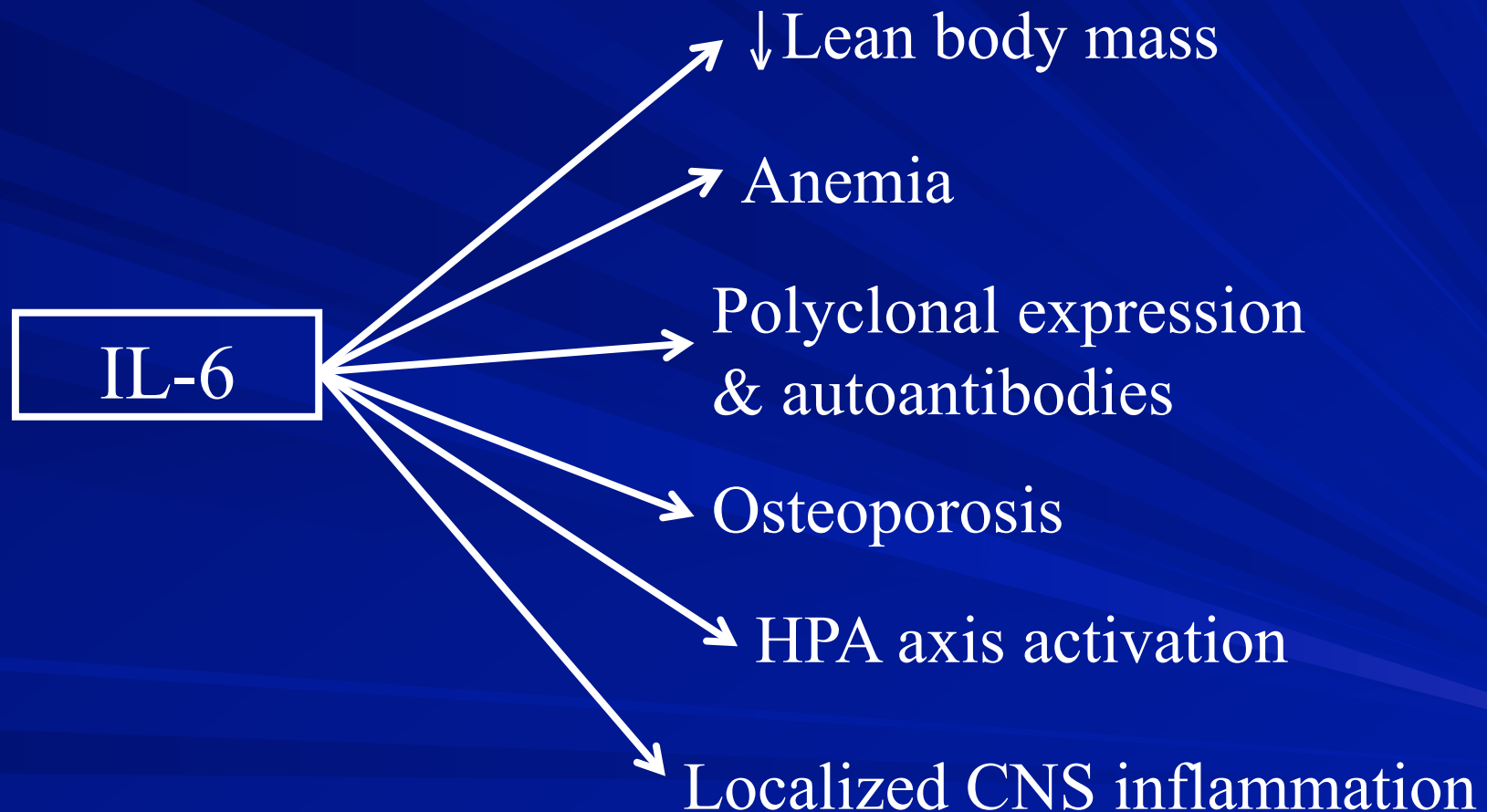
■ Chronic Inflammation

- Modest elevation of cytokines and WBC
- IL-6 most associated with adverse outcomes
- Threshold of 2.51pg/ul for adverse outcomes

Inflammatory Mediators and Aging



IL-6 and Multisystem Dysregulation



Best Serum Inflammatory Markers of Vulnerability

- In CHianti and Cardiovascular Health Study samples and phenotypic data
- Baseline serum cytokines measured first in In CHianti
- Determined relationship between cytokines and mortality
- Validated Findings in CHS

Best Serum Inflammatory Markers of Vulnerability?

- Candidate Inflammatory Biomarkers
 - IL-1 RA
 - IL-6, 15, 18, 1beta
 - TNF-alpha and R1, R2
 - CRP
 - MCP-1

Five Finalists Based on Mortality and Age Association

- IL-1 RA
- IL-6
- TNF-alpha R1
- IL-18
- CRP

Endophenotype Development

- Three methods utilized and evaluated for mortality risk analysis of inflammatory phenotypes in 10 years CHS survival data.
- Validate same method in an independent study - 10 years InChianti data

Weighted Summary Score (WSS)

$$WSS = \sum_{k=1}^5 w_k (Y_{ik} - \bar{Y}_k)$$

$$w_k = \frac{1/\sigma_k}{\sum_{k=1}^5 (1/\sigma_k)}$$

- Where Y_{ik} is each log cytokine
 $k = \text{cytokines, } 1, 2 \dots 5; i = \text{obs, } 1, 2 \dots n, n = \text{total obs.}$
- mortality risk assessed using age adjusted Cox model
- Weights are:

logCRP	logIL6	LogTNFR1	logIL18	logIL1RA
0.08	0.24	0.37	0.18	0.13

Principle Component Score (PCS)

- Uses the first principle component of correlation matrix

$$PCS = \sum W_k * Y_{ik}$$

- Where W_k is the loading of the first principle component .
 $k = \text{cytokines}, 1, 2 \dots 5;$

- $\sum w_k^2 = 1$ by the property of principle component.

- Weights (loading) are:

logCRP	logIL6	logTNFRI	logIL18	logIL1RA
0.48	0.50	0.44	0.31	0.47

Mortality Risk Score (MRS)

- Model selection for 5 cytokines by BIC

where $k=0$ is for age, $k=1, 2...5$ for cytokines

$$h_i(t) = h_0(t) \exp(\beta_0 Y_{i0} + \beta_1 Y_{i1} + \dots + \beta_k Y_{ik})$$

- IL6 and TNFaR1 are selected by strength of prediction, others dropped from model
- mortality risk score assessed using age adjusted Cox model

$$\text{MRS} = \beta_{\log\text{IL6}} * \log\text{IL6} + \beta_{\log\text{TNFa}} * \log\text{TNFa}$$

- Weights (coefficients) :

$\beta_{\log\text{IL6}}$
0.48

$\beta_{\log\text{TNFaR1}}$
0.94

Mortality Risk Score in CHS

Parameter	Chi-Square	Pr > ChiSq	Hazard Ratio
logCRP	72	<.0001	1.22
logIL6	287	<.0001	1.44
logTNFRI	274	<.0001	1.48
logIL18	24	<.0001	1.12
logIL1RA	56	<.0001	1.19
age	772	<.0001	1.8
WSS	281	<.0001	1.47
PCS	237	<.0001	1.43
MRS	433	<.0001	1.64

- Each predictor is adjusted by age, except age by its own.
- To make HRs comparable between predictors, all predictors are standardized.
- From looking at the hazard ratios for age, the model indicates that increase 1 unit of standardized age, the rate of mortality increases by 80 %.

Validation in In CHIANTI

Parameter	Chi-Square	Pr > ChiSq	Hazard Ratio
logCRP	24	<.0001	1.3
logIL6	19	<.0001	1.26
logTNFAR1	25	<.0001	1.32
logIL18	16	<.0001	1.25
logIL1RA	18	<.0001	1.29
age	366	<.0001	2.78
WSS	33	<.0001	1.23
PCS	27	<.0001	1.24
MRS	33	<.0001	1.37

- Each predictor is adjusted by age, except age by its own.
- To make HRs comparable between predictors, all predictors are standardized .
- From looking at the hazard ratios for age, the model indicates that increasing 1 unit of standardized age, the rate of mortality increases by 178%.

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