

Research Agenda for Frailty in Older Adults: Toward a Better Understanding of Physiology and Etiology: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults

Jeremy Walston, MD,* Evan C. Hadley, MD,[†] Luigi Ferrucci, MD, PhD,[‡] Jack M. Guralnik, MD, PhD,[‡] Anne B. Newman, MD, MPH,[‡] Stephanie A. Studenski, MD, MPH,^{§||} William B. Ershler, MD,[¶] Tamara Harris, MD,[†] and Linda P. Fried, MD, MPH*

Evolving definitions of frailty, and improved understanding of molecular and physiological declines in multiple systems that may increase vulnerability in frail, older adults has encouraged investigators from many disciplines to contribute to this emerging field of research. This article reports on the results of the 2004 American Geriatrics Society/National Institute on Aging conference on a Research Agenda on Frailty in Older Adults, which brought together a diverse group of clinical and basic scientists to encourage further investigation in this area. This conference was primarily focused on physical and physiological aspects of frailty. Although social and psychological aspects of frailty are critically important and merit future research, these topics were largely beyond the scope of this meeting. Included in this article are sections on the evolving conceptualization and definitions of frailty; physiological underpinnings of frailty, including the potential contributions of inflammatory, endocrine, skeletal muscle, and neurologic system changes; potential molecular and genetic contributors; proposed animal models; and integrative, system biology approaches that may help to facilitate future frailty research. In addition, several specific recommendations as to future directions were developed from suggestions put forth by participants, including recommendations on definition and phenotype development, methodological development to perform clinical studies of individual-system and multi-system vulnerability to stressors, development of animal

and cellular models, application of population-based studies to frailty research, and the development of large collaborative networks in which populations and resources can be shared. This meeting and subsequent article were not meant to be a comprehensive review of frailty research; instead, they were and are meant to provide a more-targeted research agenda-setting process. *J Am Geriatr Soc* 54:991–1001, 2006.

Key words: frailty; multisystem decline; pathophysiology

Medical practitioners have often used the term “frailty” to characterize the weakest and most vulnerable subset of older adults. Recent research efforts have helped to better define clinical and physiological characteristics of frailty and to highlight the vulnerability of frail, older adults to poor health outcomes.^{1–4} This article reports on the 2004 American Geriatrics Society/National Institute on Aging (AGS/NIA) Conference on a Research Agenda on Frailty in Older Adults. The purpose of this conference was to bring together clinical and basic science investigators from a wide variety of aging research fields to summarize the state of the art in frailty research and to identify important new directions for investigation into the pathophysiology and etiology of frailty and into potential treatment and prevention options for frail, older adults. Although the field of frailty research is in an early stage, a premise for convening the meeting was that investigation into its underlying etiologies and the development of new treatment modalities could have a profound effect on improving health and well-being for this most vulnerable subset of older adults. This conference was primarily focused on physical and physiological aspects of frailty. Although social and psychological aspects of frailty are critically important and merit future research, these topics were largely beyond the scope of this meeting.

From the *Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland; [†]National Institutes on Aging, Bethesda, Maryland; [‡]Department of Epidemiology, Graduate School of Public Health, and [§]Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; ^{||}Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Pittsburgh Healthcare Center, Pittsburgh, Pennsylvania; and [¶]National Geriatrics Resource Consortium/Institute for Advanced Studies in Aging and Geriatric Medicine, Washington, DC.

Address correspondence to Jeremy D. Walston, MD, John R. Burton Pavilion, 5505 Hopkins Bayview Circle, Baltimore, MD 21224.
E-mail: jwalston@jhmi.edu

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CLINICAL OVERVIEW OF FRAILITY

Most practitioners of medicine have been trained to focus on specific medical diseases when approaching a patient. Frailty does not fit neatly into that practice pattern, because it is almost never the basis for a “chief complaint,” and its presence is often subtle or asymptomatic.⁵ Instead, frailty is evident over time through an excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event. Lack of clinical focus on frailty may be due, in part, to the likelihood that frailty is currently identified through characteristics that are directly related to physical function and that at the same time are consequences of the accumulation of subclinical conditions, acute and chronic disease, and behavioral and social risk factors.⁵ When caring for older adults, it is apparent that there is a spectrum of resilience, from most frail and vulnerable to highly independent and robust.⁶ Such vulnerability can exist in the presence or absence of disease and disability and lies at the heart of frailty. Three clinical cases, outlined below, illustrate this spectrum and help highlight the concept of frailty as an independent entity with altered physiology at its base.

Case 1: A 75-year-old man with a history of congestive heart failure, knee osteoarthritis, and hypertension presented for elective knee replacement. He lifted weights regularly and walked up to 2 miles per day before his knee pain worsened over approximately 2 months. His elective knee replacement was without complication, and he returned home taking narcotic pain relievers and with home physical therapy 72 hours after undergoing surgery.

Case 2: A 75-year-old man with history of congestive heart failure, knee osteoarthritis, and hypertension presented for elective knee replacement. He volunteered regularly but had been feeling less able to do so lately because of knee pain and fatigue. His elective knee replacement was performed without complications. On postoperative Day 1, he became delirious while taking low-dose narcotics, and fell while trying to get out of bed. He developed incontinence, and refused to participate in physical therapy. On postoperative Day 5, he was transferred to a subacute rehabilitation unit, where his delirium slowly resolved. He required 2 full weeks of in-patient care and a month of outpatient rehabilitation to regain mobility and independence.

Case 3: An 82-year-old man presented to the emergency department after a neighbor found him on the floor. The patient had a nonsyncopal fall in 1999 with a femoral neck fracture and successful repair; osteoarthritis in the hips and hands; and a 15-pound weight loss over the previous year. He was still grieving the loss of his wife 3 years earlier. He lived alone, and friendly neighbors cared for him. Diagnostic examination revealed nothing abnormal except diffuse muscle weakness and unsteady gait. He had muscle wasting without focal neurological deficits, was cognitively intact, and had no other symptoms or signs of major depression except weight loss. After 3 days in the inpatient hospital, he was transferred to a subacute rehabilitation facility for further care. After 2 weeks, he could walk 30 feet with a walker but was unable to care for himself. He was transferred to an assisted living facility, where he died 3 months later.

The spectrum of susceptibility and clinical stability of these three patients strongly affected their clinical out-

comes. The first and second patients appeared equally robust before undergoing surgery; the second was more vulnerable to delirium and functional decline and did not do as well in his postoperative recovery period. Frailty in the third patient was evident before the fall, and his vulnerability and the outcomes of loss of independence and mortality are consistent with the current conceptualization of frailty. The clinical observations made during their hospitalizations and outpatient stays and questions about how these difficulties could have been identified and treated highlights the following questions.

- What were the physical and physiological differences between these three individuals?
- Are there ways to identify physiological vulnerability and risk before the appearance of poor outcomes?
- What is the underlying biology that makes some patients more vulnerable to poor outcomes than others?
- What interventions might be effective in preventing or reducing vulnerability to poor outcomes in this specific group of older patients in addition to what is already known about care and prevention in older patients?

These questions were central to the purpose of this AGS/NIA conference on frailty and helped to provide guidance for the development of a future research agenda on frailty.

CONCEPTUALIZATION OF FRAILITY AND ITS PHENOTYPES

The term “frail” has varied clinically relevant vernacular meanings (e.g., easily broken or destroyed; likely to fail or die quickly; unusually susceptible to disease or other infirmity; lacking normal strength or force; weak, tenuous, thin, and slight). There is a wide range of common phenotypes in geriatrics to which such terms may be related, including muscle weakness, bone fragility, very low body mass index, susceptibility to falling, vulnerability to trauma, vulnerability to infection, high risk for delirium, blood pressure instability, and severely diminished physical capabilities, although the word “frailty” in the common notation of clinical geriatric medicine usually describes a condition in which a critical number of these specific impairments occurs in parallel.

Nevertheless, researchers have applied differing conceptual approaches describing these phenomena. As discussed in a recent editorial,⁷ differing concepts and definitions of frailty have included a variety of domains, including physical characteristics and function, cognitive function, other psychological characteristics, and psychosocial factors. One general conceptual issue regarding frailty relates to the utility of its definition as a single syndrome versus definitions of frailty related to a diverse range of clinical traits associated with aging. These are discussed below.

Frailty as a Single Syndrome

Numerous investigators and several working groups on frailty have hypothesized that frailty is a clinical syndrome. Proposed syndrome definitions are based on the presence of some or all of set of specified symptoms and signs. Differing syndrome definitions of frailty have included various com-

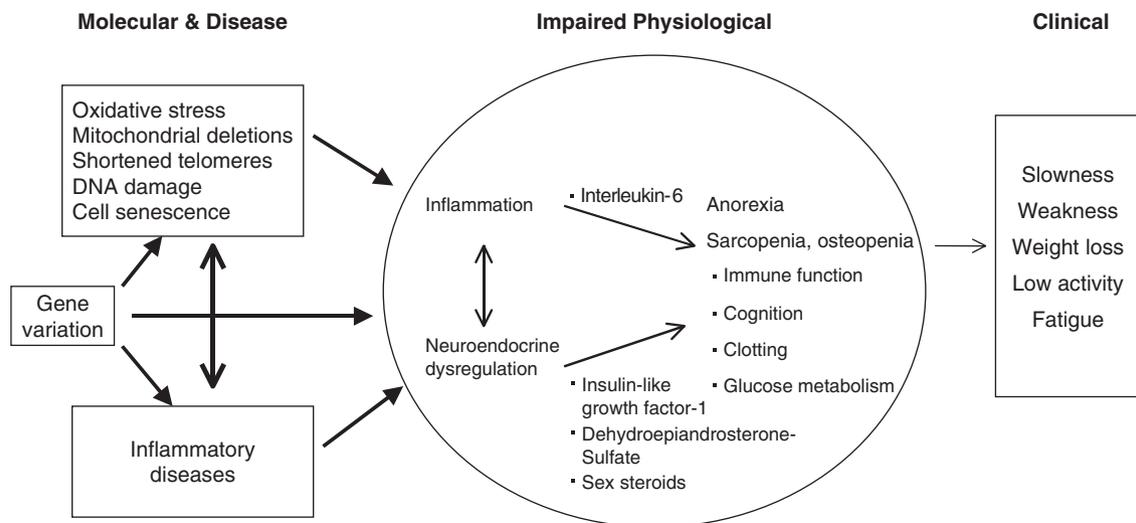


Figure 1. Overview of hypothesized molecular, physiological, and clinical pathway to frailty.⁵ This modal pathway illustrates possible or probable connections between molecular, physiological, and functional decline that were discussed at the meeting. Arrows pointing in both directions illustrate potential interactions between systems.

binations of the following: weakness, fatigue, weight loss, decreased balance, low levels of physical activity, slowed motor processing and performance, social withdrawal, mild cognitive changes, and increased vulnerability to stressors.^{1,5,8,9} By definition, manifestations associated within a syndrome occur in combination, and no single manifestation is sufficient to identify those with the syndrome. A consensus report from a group of Italian and American geriatricians has been published advocating that criteria to define physical frailty be based on impairments in physiological domains that include mobility, balance, muscle strength, motor processing, cognition, nutrition (often operationalized as nutritional status or weight change), endurance (including feelings of fatigue and exhaustion), and physical activity.³

Other working groups have established the predictive validity of proposed syndromic definitions of frailty for outcomes in populations of older adults. One found that a combination of inactivity and weight loss was a significant predictor of disability and mortality.² Another developed screening criteria for frailty as a syndrome requiring the presence of a critical mass (≥ 3) of the following clinical manifestations: weakness, weight loss, slow walking speed, fatigue, and low levels of activity.¹ This phenotype has been found to predict various poor clinical outcomes, including falls, the development of disability, hospitalization, and mortality.¹ This validation study also showed that, although frailty frequently exists concurrently with disease and disability, it is independent and distinct from these characteristics.¹ These frailty criteria have further been shown to be associated with specific alterations in physiological variables, including inflammatory biomarkers, altered glucose metabolism, and markers of clotting processes,¹⁰ providing evidence of multisystemic involvement. Although the clinical manifestations of frailty summarized in this phenotype are not identical to those measured in other studies, mobility, strength loss, and weight loss are components of frailty phenotypes in other national and international working groups.^{1–4} Consistent with this approach, a Clinical Global Impression Measure for Frailty

that includes intrinsic domains of mobility, strength, endurance, nutrition, and neuromotor performance was recently developed and is being validated.⁴

Because many of the symptoms and signs referred to in prior studies of frailty are known to be physiologically related to one another, they provide a conceptual link between molecular alterations associated with aging, physiological decline, and the clinical systems that are part of a hypothesized “phenotype” of frailty. These biological connections are organized conceptually in Figure 1, which shows the hypothesized relationship between molecular, physiological, and clinical variables discussed at this conference that in the aggregate are hypothesized to constitute frailty.

Frailty: One or Multiple Phenotypes

At the conference, alternatives to the concept of frailty as a single entity were presented. The general usage of “frailty” subsumes a diversity of vulnerabilities, weaknesses, instabilities, and limitations (which span a considerably more diverse range than those discussed in the preceding paragraphs). These traits do not always occur together but are found individually and in various combinations. There is only limited knowledge about the degree to which they share common causes or effects. From this perspective, the relative utility of a definition of frailty as a single entity, versus definitions of individual vulnerabilities, weaknesses, instabilities, and limitations or of various clusters of such traits, remains unclear pending additional data and further analyses.

These considerations suggest the value of empirical strategies to identify clusters of vulnerabilities, weaknesses, instabilities, and limitations with shared causes. Such clusters could be used as syndromic definitions of one or more “frailties” that encompass the set of related clinical phenomena in the cluster, as illustrated in Figure 2. Analogous approaches using more-sophisticated analytical techniques are available. Given the large number of possible clusters, it would be useful to determine which, if any, combinations of such traits are especially likely to share common contrib-

Contributory factors	1	x		x	
	2			x	
	3		x		
	4		x		x
		A	B	C	D

Vulnerabilities, weaknesses,
instabilities, limitations

Figure 2. Schematic of findings from hypothetical study or studies of four specific traits (vulnerabilities, weaknesses, instabilities, and limitations) and four factors potentially contributing to them. Xs refer to positive findings of association between specific factors and specific traits. Findings indicate that traits A and C have in common etiological factors 1 and 2 (and not 3 or 4) and that traits B and D have in common factors 3 and 4 (and not 1 or 2), suggesting two possible clusters of “frailties” with distinct and different pathophysiologies or etiologies.

uting factors. One approach would be to identify combinations that occur more commonly than would be expected by chance, using simple binomial approaches, factor analyses, or other methods. (Because of the high prevalence of many individual frailties, chance combinations would not be rare.) This approach might reveal important previously unidentified factors contributing to multiple frailties.

Strategies to identify clusters of vulnerabilities, weaknesses, instabilities, and limitations that could be useful as broader frailty phenotypes could also benefit from multifactorial approaches to elucidate factors contributing to each of these individual traits. Such factors include currently known risk factors for various conditions and other putative genetic, cellular, physiological, psychological, or sociobehavioral factors. Studies of factors with effects on multiple traits and physiological systems (e.g., hormones or cytokines) might also reveal clusters.

The value of research on individual traits and empirical identification of clusters is not inconsistent with the possibility that a broader definition of frailty may be useful, and even crucial, in research to understand the causes and consequences of the variety of traits subsumed under the general idea of frailty. It is possible that a single frailty syndrome that consists of biologically related traits will, ultimately, be found. Ultimately, findings from either approach will help strengthen conclusions related to the underlying biology of frailty.

TOWARD A BETTER UNDERSTANDING OF THE PHYSIOLOGY OF FRAILITY AND THE BIOLOGY OF VULNERABILITY

Given the overlap of clinical domains for physical frailty consistently identified across several independent working groups, discussion at the conference turned to potential connections between the clinical realm of declines in strength, endurance, and weight and the hypothesized physiology that might underlie these clinical changes. In addition, given the vulnerability to the development of poor health outcomes in frailty associated with these changes, participants discussed the potential etiologies of this vul-

nerability, including the multiple interrelated physiological and molecular system changes hypothesized to contribute to this vulnerability observed in frailty.

An important concept that was highlighted throughout the conference was the critical balance between stability and vulnerability. Discussions of nonlinear dynamics and chaos theory provided new insights into how investigators might detect and quantify changes at the physiological and molecular level. It was suggested that, in vital and resilient organisms, complex physiological pathways allow a wide variety of adaptive responses that are qualitatively and quantitatively modified to specific events. This complexity helps keep multiple systems in balance with minimal fluctuations in the homeostatic equilibrium. Aging results in the decline of normal interactions and the redundancy of communication between these physiological systems. It was hypothesized that frailty, both the phenotype and its latent vulnerability, results from reaching a threshold of decline in one or more systems that triggers a cascade of dysregulation in multiple systems and that this dysregulation may influence many clinical domains, as well as comorbid conditions and disability.

One speaker hypothesized that the decline in complexity of response to stimuli observed in aging and perhaps in frailty may be, in part, due to loss of complexity in fractal patterns.¹¹ Fractals are geometric subunits that resemble larger-scale units. Many anatomical structures and physiological processes such as alveoli, neural networks, and bony trabeculae have such repeating subunits and therefore fractal properties. It was theorized that, in part, a progressive loss of complexity in the fractal architecture of anatomic structures and dynamics of physiological processes can characterize both aging and frailty.¹² This loss of structural and functional complexity may impair an organism's ability to communicate within and between systems and to adapt to stress. In addition, most physiological systems have an ability to undergo reactive tuning, which enables normalization after periods of physiological stress by creating a new state of equilibrium that is different from the one that existed before the perturbation. It was hypothesized that this retuning may not be possible with loss of complexity and that this may result in the vulnerability to further decline and poor outcomes seen in frailty.

Several conference participants emphasized that the study of linear declines in individual biological parameters may not be sufficient to further explore the multiple system declines hypothesized to underlie frailty; rather, frailty may develop in the presence of a critical mass of systems being affected sufficiently to undermine the ability to maintain homeostasis. If this is correct, then new analytical approaches involving nonlinear dynamics may be critical to improving the biological understanding of multiple system declines hypothesized to underlie frailty.¹²

CLINICAL ILLUSTRATIONS OF MULTISYSTEMIC DECLINE AND VULNERABILITY

Participants presented illustrations of the concept of vulnerability and multisystem decline using data from clinical observations and clinical studies. First, the pathophysiological stressors of surgery and anesthesia, which activate stress response pathways, may trigger complications fre-

quently seen in frail older adults.¹³ Physiological systems hypothesized to play a role in this vulnerability include the central nervous system (CNS), the sympathetic nervous system (SNS), endocrine system responses from the pituitary gland and the adrenal gland, and innate immune system responses. It was hypothesized that a frail individual who already has compromised regulation within and across these systems may have more difficulty than others in tolerating surgical stress. Another clinical example of system decline that may be relevant to physiological vulnerability and frailty is the failure to adapt to neuromuscular stressors that may underlie incremental development of gait instability and resulting increased fall risk.^{14,15} One of the speakers further suggested that studies of fractal declines in each individual system involved in mobility, with use of new analytical and measurement techniques that capture the nonlinear interactions between these systems, may shed further light on the biology of vulnerability.

During the conference, other clinical examples were presented that are consistent with the theory that multisystem change underlies frailty. These included evidence for the activation of thrombotic pathways, either at baseline or in the physiologically stressful setting of infection or disease that triggers inflammatory mediators and their independent associations with frailty (as defined by some investigators) and of other poor health outcomes.^{10,16} The hematopoietic system was also discussed as one that stress responses from multiple systems may influence and that may be altered in frailty.¹⁷ Increasing evidence suggests that mild anemia not related to iron or B₁₂ deficiency is frequently observed in a subset of older adults. Multiple physiological inputs, including increased inflammatory mediators, blunted production of and response to erythropoietin, and failed production of other hematopoietic growth factors may trigger this condition. A study of older women found that those with lower hemoglobin levels are also at greater risk for mortality.¹⁸ Because of the nonlinear, and complex, interactions between these physiological systems, it has been difficult to identify specific triggering mechanisms in increasing inflammatory mediators and clotting processes observed cross-sectionally in at least one frailty phenotype.^{10,19} Conference participants urged future focus on etiological triggers and evaluation of new methodology to address interactions between systems.

BODY COMPOSITION IN FRAILITY: THE ROLE OF MUSCLE AND FAT IN MULTISYSTEM DYSREGULATION

It has long been hypothesized that sarcopenia, or aging-related loss of skeletal muscle, is an integral component of frailty and its clinical hallmark. It is perhaps also the best studied of all contributing physiological systems that are postulated to decline in frailty. As with the systems discussed above, the maintenance of skeletal mass is a function of multiple factors including hormonal, inflammatory, neurological, nutritional, and activity components.^{20,21} Thus, the development of sarcopenia can, in itself, be a result of alterations in multiple physiological systems, as well as from declines in activity and specific disease.

Researchers have also found large discrepancies between muscle mass and the amount of force generated by

muscles. The magnitude of such discrepancy tends to increase with age. With development of research on macroscopic, microscopic, and functional changes in human tissues, there is now increasing evidence to indicate that fat infiltration of muscle may explain in part the discrepancy between mass and force.²² Although the understanding of the natural causes, consequences, and implications of muscle fat infiltration is limited, one possibility is that it reflects alterations in differentiation of progenitor cell populations, particularly the appearance of mesenchymal adipocyte-like cells in muscle and other tissues.²³

It has been recently recognized that intramuscular fat has metabolic characteristics similar to those of visceral fat; this could be important, because in some individuals, the amount of total body intramuscular fat is equivalent to the amount of visceral fat. These metabolic characteristics include endocrine and paracrine activities, including the secretion of hormones and inflammatory markers such as interleukin (IL)-6. It is hypothesized that IL-6 and other inflammatory mediators contribute to frailty.^{10,24} Metabolically active fat depots in any location could induce a chronic inflammatory state that could exacerbate sarcopenia and ultimately contribute to frailty. The hypothesis that obesity or diabetes mellitus could be etiological factors in, as well as predictors of, frailty was discussed, as well as the potentially distinct subset of frail individuals previously characterized by the term “sarcopenic obesity.”^{25–27} Participants recommended further investigations of the relationships between obesity, diabetes mellitus, and glucose as a continuous variable with a recommendation for mechanistic studies that connect these associations to biological mediators.

POTENTIAL ROLE OF THE NERVOUS SYSTEM IN FRAILITY

There is evidence that a major factor leading to sarcopenia (i.e., age-associated loss of muscle mass) is the reduction of the number of alpha-motorneurons, which results in lower background electrical stimulation of the muscle fibers,²⁸ although the specific mechanism of this process of involution, and whether it is related to lipid infiltration of muscles, is poorly understood. Additionally, declines in muscle mass or function may result from pathology in the CNS, which contributes to multisystem dysregulation.

The CNS is highly plastic and adaptable and plays a major role in compensation. Given this plasticity, the brain could be at the center of a vicious cycle of events stemming from a generic, initial impairment and leading to an accelerated decline of physical function. Observational studies provide evidence of the existence and importance of a cycle of decline in older, but apparently healthy, individuals. For example, signs of neurological dysfunction are frequently detected in older persons free of any diagnosis of neurological disease.²⁹ The presence of such neurological signs are associated with poor lower extremity function, falls, and reduced physical activity.³⁰ Finally, reduced physical activity, through its effect on inflammation and insulin resistance, can exacerbate neurological damage.³⁰ These declines in physical activity, along with inflammation, in combination with other neurological deficits, may contribute to the development of the physiology of frailty. Recogn-

dition of this vicious cycle could present multiple therapeutic targets for treatment that might slow the process that, although initiated by specific pathology, may lead to frailty.

Although the role of the CNS in manifestations of frailty requires further demonstration, many neurological diseases determine problems in gait, balance, strength, and nutrition, all of which are considered central components of frailty. The potential for a neurological basis or core components of frailty suggests that studies of frailty in older adults should assess associations with psychomotor slowing, slowed ability to perform in dual cognitive–physical tasks, and inability to block distractions. Parallel information on the autonomic nervous system could provide information on adaptability and plasticity. Given the importance placed on the development of dynamic testing to better understand frailty, it was suggested that there are validated provocative tests to characterize neurological–cognitive vulnerability that could be considered as tests for frailty. Hierarchically, these include a simple reaction test (e.g., alertness); a performance test (e.g., gait); adding distraction to the simple reaction or performance tests, such as pleasant and unpleasant noise and additional tasks such as calculating; and measuring autonomic functions simultaneously in response to a stress test.

In summary, the complex interactions of many physiological systems and of body composition are influenced by, or influence, the CNS and SNS. Neurological dysfunction may further affect these interactions, which might contribute to the hypothesized multisystemic basis of frailty, which is manifested in unstable homeostasis and, ultimately, decompensation in the presence of stressors. Studies are needed to test the hypothesis that aggressive forms of training and rehabilitation can alter frailty.

THE INTEGRATED PATHOPHYSIOLOGY OF FRAILITY

As described in previous studies, many of the physiological systems thought to decline in frailty are those that function in communication. Increasing evidence suggests that specific inflammatory cytokines and bioactive hormones, as well as intact SNS and CNS function, are critically important in maintenance of skeletal muscle and a host of molecular and physiological changes that may contribute to the development of frailty.¹⁷ Specific evidence regarding pathophysiological changes in the innate immune and endocrine systems, and interactions between these critical physiological systems, may help investigators identify crucial triggering mechanisms that lead to nonlinear multisystem declines in frailty. Figure 1 illustrates a conceptual framework of specific physiological system changes that may contribute to the underlying vulnerability and the clinical manifestations of frailty.

Evidence was presented that supports an important role of inflammation in at least one definition of frailty. In cross-sectional association studies performed in at least three different populations, significant positive relationships were identified between frailty and the inflammatory cytokine IL-6, C-reactive protein, and greater numbers of monocytes, and total white blood cells,^{10,24,31} Higher levels of these same inflammatory cytokines correlate with greater

vulnerability to disability and mortality, further supporting a role for these biologically active molecules and systems in the development of poor health outcomes.³² Although none of the mean values of inflammatory markers observed in frailty appear to reach the high levels observed in inflammatory diseases such as rheumatoid arthritis or malignancy, they are suggestive of a chronic, low-level activation of inflammatory mechanisms in frail older adults.

Multiple lines of evidence demonstrate a biological link between elevated IL-6 and bone and muscle loss, anemia, insulin resistance, and altered immune system modulation and hypothalamic–pituitary–adrenal axis stimulation, making it less likely that IL-6 is simply a benign biological marker.¹⁷ The regulation of IL-6 and inflammatory processes are complex, with a network of interacting cytokines, including tumor necrosis factor (TNF)- α , IL-1 β , IL-10, and interferon gamma, all of which are probably important in mechanisms that control inflammation. Inflammation occurs through the activation of common molecular pathways in several interactive physiological systems, including clotting cascades, the complement system, the immune system, and endothelial cells playing active roles.¹⁹ Specific components of these systems can be measured in the serum and may be further characterized in response to external or internal stressors. Given the influence of inflammatory mediators in multiple physiological systems, the study of the interactions between cytokines, the identification of specific inflammatory triggers in frailty, the identification of the source of cytokines through cell or tissue-specific biomarkers, the interactions between inflammatory cytokines and the endocrine, neurological, and hematopoietic systems and the development of tests to measure change in the face of physiological stressors were suggested to be of high priority in research on the etiology of frailty.

Like the inflammatory system, the endocrine and neuroendocrine systems are composed of several separate, but related, organs or tissues that secrete specific hormones and stimulate components of the CNS and SNS that regulate multiple physiological processes. It has frequently been postulated that the sex steroids and the growth hormone axis contribute to aging-related changes in body composition and, potentially, to frailty.¹⁷ The decline in these hormone levels also triggers inflammatory mediator transcription and interactions between endocrine and inflammatory systems.¹⁷ Trajectories in the declines of each of these hormones may prove predictive in the development of frailty but have yet to be studied. Effects on frailty of these hormonal changes may be mediated through skeletal muscle declines, appetite changes, or activation of inflammatory pathways.³³

The adrenal androgen dehydroepiandrosterone-sulfate (DHEA-S) and the growth hormone messenger molecule insulin-like growth factor (IGF)-1 decline with age. Low levels of DHEA-S and IGF-1 are associated with frailty defined as a composite syndrome of a critical mass of deficits in strength, endurance, weight loss, walking speed, and physical activity.³⁴ IGF-1 plays an important role in the development of skeletal muscle cells and is likely an important factor in muscle mass maintenance with increasing age. There is also evidence of interaction between IGF-1 and IL-6, which suggests that inflammation may drive IGF-1 levels down or downregulate its biological sensitivity.³⁵

Furthermore, increasing evidence suggests that DHEA-S suppresses inflammation induced by nuclear factor kappa B (NFkB).³⁶ Hence, lower levels of DHEA-S observed in frailty may contribute to chronic inflammation and ultimately to frailty.

Interactions between inflammatory cytokines, endocrine systems, CNS/SNS activity, and skeletal muscle have been observed in human and animal studies. There is a large body of specific inflammatory disease literature that suggests that circulating inflammatory mediators, such as IL-6, TNF- α , and IL-1 β , trigger the loss of total body cell mass in those with inflammatory disease, perhaps via apoptotic pathways.³² In addition, there is evidence that inflammatory cytokines such as IL-6 may interfere with anabolic function of sex steroids and growth hormone.^{37,38} Conversely, it is also likely that loss of estrogen, and perhaps testosterone, leads to the uncovering of important inflammatory gene transcriptional elements, leading to increased production of IL-6 and other inflammatory mediators in several cell types.¹⁷ Cortisol elevations dampen inflammation in part but also contribute to declines in skeletal muscle. Longitudinal study designs in subjects who are of advanced age but not yet frail would prove beneficial in the identification of causality in the decline in hormonal production or effectiveness of communication and increased inflammation observed in frail older adults. In addition, alterations in any of these systems may prove useful in newer analytical methods that attempt to further define the nonlinear dynamics that are hypothesized to underlie frailty.

BIOLOGICAL MECHANISMS AND THE MOLECULAR BIOLOGY OF FRAILTY

Throughout the conference, declines or altered function in multiple physiological systems were described in relationship to frail older adults.^{10,17} The underlying causes for these multisystemic physiological declines are unclear, but genetic variation and age-related molecular changes may provide the basis for understanding the physiological decline observed across systems. This section of the conference discussed the potential relevance of several basic mechanisms in the biology of aging to the development of frailty. This included cellular senescence, loss of telomeric structures, mitochondrial dysfunction, increased free radical production, and poor deoxyribonucleic acid (DNA) repair capability. It was stressed that this area has largely been unexplored in human frailty research and represents an area of emerging importance in the transitional research realm with enormous opportunities for discovery. A brief summary of presentations and discussion follows.

Mitochondria are intracellular organelles found in all cell types that are critical to the generation of cellular energy via oxidative phosphorylation. Oxidative stress mostly determines age-related changes in mitochondrial DNA, which have been postulated to trigger abnormal function of mitochondrial proteins, resulting in the generation of greater levels of free radical molecules, such as superoxide. The course of this progressive mitochondrial impairment is probably not linear and is strongly accelerated when a critical mass of DNA damage occurs. Chronic production of higher levels of free-radical molecules, and an accompany-

ing shift in cellular redox potential, may lead to altered gene expression and damage to existing lipids and proteins.³⁹ In addition, increased levels of the free radical hydrogen peroxide directly trigger activation of inflammation and transcription of biomediators via NFkB pathways.⁴⁰ The generation of free radicals can also be highly toxic to other parts of the cell. For example, genomic DNA is regularly exposed to high levels of oxidative stress, which in turn, may facilitate DNA strand breaks, formation of protein-DNA crosslinks, and ultimately, altered gene expression in many tissues.⁴¹ It was hypothesized that mitochondrial biology and the production of free radicals play an important role in the decline of multiple physiological systems and potentially represent important areas for future frailty research.

Recent developments in the understanding of telomere biology also show important potential toward improved understanding of the altered biology from which frailty may develop. Telomeres are the repetitive DNA sequences and specialized proteins that cap and protect the ends of linear chromosomes. As organisms age and cellular reproduction cycles mount, these capping structures shorten, and this, in turn, can trigger a cellular DNA damage response and ultimately apoptosis, cellular senescence, or genomic instability and the generation of abnormal proteins.⁴² Early translational studies have indeed demonstrated that age-matched older adults with the shortest telomeres died, on average, 5 years earlier than those with the longest telomeres.⁴³ Although the exact mechanism by which shortened telomeres lead to early mortality is not known, studies of the molecular and tissue pathophysiology that results from shortened telomeres may be applicable to the study of the biology of frailty.

The study of the etiology of cellular senescence, and the altered physiology of senescent cells, are also promising areas for future biology-of-frailty research. Oxidative stress, DNA damage related to oxidative stress or environmental causes, and dysfunctional telomeres can induce cell senescence.⁴⁴ Senescent cells are, in general, in an irreversible growth arrest phase but are at the same time resistant to apoptosis. It is increasingly apparent that these senescent cells have altered function and are not simply passive bystanders in metabolic processes. For example, senescent fibroblasts are known to disrupt growth and differentiation of epithelial cells and potentially promote the development of disease states such as cancer. In addition, senescent fibroblasts secrete inflammatory cytokines, which in turn may contribute to the pathophysiology of frailty. Many other cell lines remain to be studied that also undergo a senescent process, potentially leading to altered function across systems and contributing to the physiology and vulnerability of frailty.

Ultimately, genetic variation in any of thousands of genes could influence the development of frailty. There are rare genetic premature aging syndromes related to poor DNA repair (Werner's syndrome) and telomere abnormalities (dyskeratosis congenita) that provide potential models for genetic studies of other gene variants in future frailty research. Methodologies are now available that allow the study of genetic variation in hundreds of genes in complex physiological pathways (i.e., inflammatory cascades, endocrine systems). Studies in large populations of older adults

may prove important in the identification of gene variation and defining the biology that may trigger altered molecular or physiological function that ultimately leads to frailty.

THE DEVELOPMENT OF ANIMAL MODELS FOR THE STUDY OF FRAILITY

The next generation of frailty research will need to include detailed etiological studies and studies of new interventions targeting specific biological pathways. To facilitate this level of biological discovery, the identification and characterization of animal models that approximate human frailty will be of critical importance. The speakers at this conference with expertise in the development of aging mouse models were posed the following question: "What are the ideal criteria for frail, old mice or rats?" It was suggested that the application of frailty criteria described earlier¹ to mouse and rat models would be a reasonable starting point (e.g., the identification of older mice or rat strains with muscle weakness, weight loss of no clear etiology, slowed performance, or low levels of activity). In addition, the use of physiological markers, such as inflammatory or endocrinological measurements, that correlate with frailty may also have utility in the identification of appropriate frail animal models. Methodologies from previously existing studies of sarcopenia in normal mice and rats and from currently used measurements of physical performance such as grip strength, body composition using computed tomography scanning, and behaviors such as activity and feeding are likely to be directly applicable to the study of frailty.

Finally, and perhaps most importantly, speakers noted that frail-animal models should demonstrate vulnerability to stressors and show evidence of dysregulation under stress. There are a number of frequently used, standardized challenges for testing stress responses, including oxidative stress, bacterial or viral exposure, and heat or cold exposure. The identification of animals with such vulnerability as having a frailty trait may greatly facilitate the identification of etiological or mechanistic underpinnings of this vulnerability; this, in turn, may be directly applicable to etiological and treatment discovery in humans.

Given the vast number of specific mouse models developed to study aging-related phenotypes and chronic diseases of older age, the speakers were asked to help identify potential frailty candidates from previously existing mouse and rat strains. Normal, wild-type animals in which features of human frailty appear with advancing age could serve as biologically appropriate models for frailty. Colonies of old normal rodents are available for pathophysiological studies, but long-term etiological studies in such strains could require 2 or more years, so a number of specific transgenic mice strains were discussed that may be useful in the study of frailty. First, the strain of mouse that lacks the *Klotho* gene is normal until 4 weeks, and then develops growth retardation, decreased activity, and early mortality. In addition, it develops many signs of an accelerated aging phenotype, with atherosclerosis, osteoporosis, emphysema, dementia, and thinning skin occurring before premature death. This mouse strain also develops hypercalcemia and calcification of soft tissues, suggesting that some specific electrolyte abnormality may be responsible, in part, for the development of this phenotype. Second, Snell

dwarf mice were put forth as a potential model for frailty. These mice have abnormally low production of growth hormone, prolactin, and thyroid stimulating hormone and have less than 25% survival of wild type in a challenge-rich environment, although in a protected environment, they do well and survive up to 35% longer than wild-type mice, highlighting the potential importance of endocrinological pathways in protection against external stressors. Third, other potential mouse models include those that have altered abilities to regulate cellular apoptosis in response to oxidative stress (p66 null mouse) and suppression of cytokine signaling. These mice have an impaired ability to turn off cytokine-stimulated signals, thus amplifying the effects of the inflammatory cytokine IL-6 and INF- γ . The resulting phenotypes include shorter survival and mild anemia. Although each of these models is compelling, each also has a unique genetic etiology for the development of the phenotype that may or may not be appropriate for the study of human frailty. Further studies of human frailty physiology will help inform the development of a better frail mouse model.

Finally, the use of data generated by calorically restricted animal models was discussed as an informative tool for biological discovery and for the identification of a frail-mouse model. Many of the positive effects of caloric restriction are exactly the opposite of the physiological observations made in frail, older adults. For example, greater insulin sensitivity and lower serum glucose, lower CNS activity, better hormone sensitivity, and better immune function are all characteristics of calorically restricted rodents.⁴⁵ Studies of interactions between these physiological systems and the identification of rodent models with declines in these systems will likely facilitate biological discovery in frailty research.

POTENTIAL FOR PHARMACOLOGICAL AND NONPHARMACOLOGICAL INTERVENTIONS: RATIONALE AND STRATEGIES FOR TREATMENT: EXPLORATORY THEORY AND EVIDENCE

Regardless of whether the conceptual viewpoint is of one frailty; a frailty syndrome; individual vulnerabilities, weaknesses, instabilities, and limitations; or a variety of clusters of such traits, understanding the etiology and pathophysiology of the trait(s) of interest is essential to establish criteria for diagnosis, including screening and early recognition, and to identify potentially effective treatment strategies and optimal intervention point(s) over the course of the development of frailty in old age. Such interventions could be targeted at frailty independent of specific diseases, and preventive or treatment interventions could be effective at a number of points before the end stage.

Interventions have been tested in older adults that target correlates or specific components of frailty. Based on intervention studies to date, physical activity, particularly strength and balance, but also endurance training, has the most apparent potential for improving physical function. Muscle mass and strength have been examined as treatment targets, and resistance exercise interventions have been shown to improve muscle strength, gait speed, and self-reported functioning. Nutritional interventions based on caloric intake alone have not been demonstrated to be

effective, although further studies of micronutrient and components of dietary intake may be useful. Potential drug interventions include anabolic hormones such as megestrol, growth hormone secretagogues, testosterone, and DHEA. Clinical trials of these agents suggest that, in the absence of exercise, they tend to increase muscle mass without improving strength or function; furthermore, side effects limit feasibility. Other novel agents such as erythropoietin, beta-2 adrenergic receptor agonists, angiotensin-converting enzyme (ACE) inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have mechanisms of effects or benefits observed that could possibly be useful in the treatment or prevention of frailty, but clear benefits for functioning have not been demonstrated in clinical trials.

Anabolic factors have been considered to be potentially important interventions for frailty, because their levels tend to decline with age and they have known effects on strength and muscle mass. Studies of DHEA and testosterone have included some frail older adults, targeting muscle mass, strength, and physical ability as outcomes, but effects on function have rarely been demonstrated. One controlled intervention study found greater strength and function in older testosterone-deficient men who received testosterone replacement.⁴⁶ Concerns remain that risk of promotion of neoplasia, prostatic hypertrophy, and other adverse events persist and may outweigh benefits. A recent Institute of Medicine recommendation favored clinical trials of testosterone in frail testosterone-deficient older men, but with strict safety measures and monitoring. Selective tissue-specific androgens may offer promising alternatives. DHEA appears to be safe, but repletion does not appear to increase strength or muscle mass.⁴⁷ A growth hormone secretagogue has been studied in an acute deconditioning model (post-hip fracture); although IGF levels clearly increased, treatment potential was limited by decrements in glucose tolerance and fluid retention and the treatment ultimately did not improve functional outcomes.

Several novel treatments were examined as potential treatments for frailty. Erythropoietin has been found to have neuroprotective and regenerative effects, in that it reduced Haldol-induced apoptosis in schizophrenia, and is now under study for limiting cell death in stroke and left ventricular remodeling during myocardial infarction.^{48,49} It has been proposed that its potential neuroprotective and regenerative effects may be useful in preventing sarcopenia and osteoporosis, as well as cognitive decline. This is in addition to its known positive effects on anemia, which have also been correlated with at least one hypothesized phenotype of frailty.²⁴ ACE inhibitors have been observed to have benefits in diabetes mellitus and poststroke beyond blood pressure-lowering effects. Specifically, observational studies show that frail older adults treated with ACE inhibitors have higher strength and muscle mass.⁵⁰ Statins were also discussed as a potential treatment for frailty because of their documented antiinflammatory effects that are independent of lipid lowering. Recent clinical trials to prevent cardiovascular disease (CVD) in older adults have examined, but have not shown benefits for, frailty-related outcomes such as disability and hip fracture or cognitive decline, but the participants in these studies have been high functioning at baseline, and outcome measures have not

been sensitive for early decline. It was suggested that statins' known side effect of myopathy be further examined at a subclinical level, although the well-documented benefits of statins for CVD prevention alone would be expected to translate into prevention of frailty by limiting the adverse effects of CVD on strength and function.

These studies indicate that several interventions can alter aspects of frailty. Many may be appropriate for future clinical trials that specifically target frailty as an outcome. Exercise, especially strength training, is the most robust intervention to improve components of frailty, including muscle strength and physical functioning. Increases in protein intake above the current recommended dietary allowance, probably in conjunction with exercise, may be needed for older people to maintain skeletal mass and increase it. Strength training combined with protein supplementation has been shown to improve strength and muscle mass in very elderly sedentary nursing home patients,⁵¹ but only exercise appears to increase strength and function; that is, nutritional supplementation without exercise was not effective. In addition to exercise approaches, individualized preventive rehabilitation therapies in frail older adults that include organized physical therapy interventions have been shown to decrease functional decline.⁵² It was suggested that further development of such combined approaches may help improve function and quality of life in frail older adults.

FUTURE DIRECTIONS

Various participants suggested a variety of directions for future research on frailty.

1. Formal agreement on standardized, preliminary criteria for a clinical phenotype of frailty, recognizing that this conference was not organized to accomplish this. Other approaches could then be compared with this. Conference participants also stated that research in the field would be significantly enhanced if such preliminary criteria were established.
2. Determination of the contributions to frailty from other clinical domains not currently included in broad definitions of frailty that may enhance predictive value and potential for etiological insights from these definitions. One example is cognitive impairment or subclinical central and peripheral neurological degeneration, which may be etiological factors, components, or correlates of frailty. Some attendees suggested that an important part of a future research agenda would be the enhancement of understanding of the role of cognition and neurodegeneration in frailty and consideration of markers of neurological impairment as part of future definitions of frailty.
3. Identification of contributors to individual impairments, vulnerabilities, weaknesses, instabilities, and limitations; identification of clusters of such traits that share common contributing factors; and determination of the predictive value of phenotypes defined by such clusters. One approach would be to identify combinations that occurred more commonly than would be expected by chance.
4. Research that would aid in assessing the utility of different phenotypes relating to frailty, including:

- (a) Determination of whether frailty constitutes a clinical syndrome.
 - (b) Evaluation of whether there is one frailty with multiple risk factors, a common ultimate cause, or both or multiple frailty phenotypes with different constellations of risk factors, etiologies, and natural histories.
 - (c) Assessment of whether there are more-precise clusters of symptoms and signs that identify frail older adults than are currently recognized.
5. Development of methods to identify physiological vulnerabilities hypothesized to be central to frailty, such as poor responses to stressors. Potential approaches could include stimulation tests or simple tests that identify those who are frail, regardless of the presence (or absence) of the clinical presentation in the stable state.
 6. Identification of subclinical components and mechanisms of frailty and relationships between the molecular, cellular, and physiological levels.
 7. Development of animal and cellular models explicitly designed for the investigation of the etiology or treatments of frailty and delineation of premature or preventable frailty.
 8. Application of large population-based studies and other clinical studies to the evaluation of contributory factors to frailty and its outcomes and characterization of the natural history of frailty.
 9. Identifying genetic, cellular, physiological, psychological, or sociobehavioral factors with pleiotropic effects on multiple vulnerabilities, weaknesses, instabilities, and limitations (e.g., studies of effects of individual hormones or cytokines and their interactions).
 10. Research on the influences of specific medical, social, and psychological conditions and their pathophysiological consequences on frailty.
 11. Determination of whether there are clusters of risk factors, such as physiological or molecular systems that are dysregulated, that most strongly identify those at risk for frailty or specific frail phenotypes and evaluation of such information for insights into potential targets for preventive or therapeutic strategies.
 12. Development of innovative analytical techniques critical to understanding the altered dynamics and important interactions that underlie the vulnerability of frailty. These are likely to include computational biology, especially nonlinear methods, and development of ability to analyze multisystem and multilevel interactions in the dynamic state.
 13. Development of large collaborative networks in which populations and resources can be shared within and across institutions for the study of frailty to enhance the range of methods and research strategies focused on frailty. Novel interactive approaches will be needed for ongoing integration of discoveries at the cellular and molecular level with those at the system and multisystem level and with clinical outcomes.

Many participants agreed that a major goal is to progress to the point where potential treatments and preventable aspects of frailty are identified and clinical trials in humans are possible. Interventions may facilitate the understanding

of the pathophysiology of frailty and the development of more-specific etiological studies. It was noted that frail older adults should be included in any future clinical trials to more clearly understand how a variety of commonly used medications might positively or negatively influence frailty and poor outcomes in older adults.³

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The AGS and NIA also sponsor a Web site (<http://www.americangeriatrics.org/research/confseries/index.shtml>) that displays information for this and other AGS-NIA-sponsored bench to bedside conference series.

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