DISCUSSION PAPER

Models, definitions, and criteria of frailty

David B. Hogan[1], Chris MacKnight[2], and Howard Bergman[3], on behalf of the Steering Committee, Canadian Initiative on Frailty and Aging*

[1]Division of Geriatric Medicine, University of Calgary, Calgary, Alberta, Canada, [2]Division of Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia, Canada, [3]Division of Geriatric Medicine, McGill University, Solidage Research Group, Jewish General Hospital, Montreal, Quebec, Canada

***Members:** Howard Bergman, MD (McGill University)
Christina Wolfson, PhD (McGill University)
David B. Hogan, MD (University of Calgary)
Francois Béland, PhD (Université de Montreal)
Christopher Patterson, MD (McMaster University)
Chris MacKnight, MD (Dalhousie University)
John Feightner, MD (University of Western Ontario)
Geoff Fernie, PhD (University of Toronto)
Réjean Hebert, MD (Université de Sherbrooke)
Jean-Pierre Michel, MD (Université de Geneve)
Fred Paccaud, MD (Université de Lausanne)

"When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean - neither more nor less."

Lewis Carroll "Through the Looking Glass"

Despite the efforts of purists, academics and dictionaries, definitions must evolve along with knowledge and concepts. The logic of words must always yield to the logic of facts they symbolize.

Rene Dubos "White Plague"

Frailty is one of those complex terms - like independence, life satisfaction, and continuity - that trouble gerontologists with multiple and slippery meanings.

Sharon R. Kaufman "The Social Construction of Frailty"

1) INTRODUCTION

In this paper we will provide an overview of various models, definitions, and criteria proposed for furthering our understanding of frailty but we will not systematically evaluate and compare them. Models are descriptions or analogies that are used to help us visualize something that typically cannot be directly observed. They are at an abstract or conceptual level. Definitions are statements expressing the essential nature of something. They should make our understanding of the topic both definite and clear. Criteria are operational definitions that outline the characterizing traits of an entity. There are overlaps and connections across the various models, definitions, and criteria proposed for frailty. Some investigators have suggested all three - a model, a definition derived from the model, and explicit criteria for recognizing frail older persons.

In addition to the above, we will examine the use of

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Correspondence: D.B. Hogan, MD, Health Sciences Center, 3330 Hospital Dr. NW, Calgary, Alberta, Canada T2N 4N1.
E-mail: dhogan@ucalgary.ca

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the word "frailty" in the medical literature over the past half-century. Because of the unsettled and evolving understanding of the complex phenomena of frailty, researchers often resort to diagrams in an attempt to clarify and communicate their thoughts. The imagery used to describe frailty will be reviewed in our penultimate section.

2) METHODS

Data for this review were identified from papers largely selected from the files of the authors. Additional references were obtained from Medline searches using the text words "frail", "frailty", and "frail elderly". Medline searches were also conducted using the MeSH term "frail elderly". Other reports were identified from the reference lists of the papers identified in the manner described above. Indices of standard textbooks in geriatrics and gerontology were searched for the terms "frail", "frailty", and "frail elderly". The material selected by the authors for inclusion was felt to represent the most relevant work dealing with the specific topic of this paper.

3) HISTORICAL PERSPECTIVE

Following is an examination of how thinking about frailty and use of the term has evolved. The record shows that the term frailty has not been employed in a consistent manner either over time or between investigators.

a) Frailty and the medical literature

The term "frail" or "frailty" in reference to older adults was rarely used before the 1980s. The first listing of the term (i.e., "frail-old") in the subject index of the *Journal of the American Geriatrics Society* dates from 1990 (1). Other terms were favored like "chronic sick", "debilitated", "disabled", "sedentary institutionalized", "incapacitated", or "functionally dependent elderly" (2-8). It was often noted by its absence. For example, in the 52-page report of the Institute of Medicine on functional dependency in the elderly, the term frailty (or frail elderly) does not appear (8). On those rare occasions where it does appear, the authors implied that the frail patient was fragile, physically weak, or in need of assistance (9-11). Explicit definitions were not provided - possibly it was assumed that everyone would have an intuitive understanding of what was meant by the term.

Since 1982, though, there has been a significant upswing in the number of publications mentioning frailty (12). Following is the number of Medline citations by year of publication found under the MeSH heading "frail elderly":

1980 or earlier:	1
1981-1985:	0
1986-1990:	36
1991-1995:	793
1996-2000:	1098
2001-2002:	724 (two years)

How did the term originate? During the 1970s the heterogeneity of the older population became more widely accepted. Monsignor Charles F. Fahey and the Federal Council on Aging (FCA) in the United States are credited with introducing the term "frail elderly" to describe a particular segment of the older population (13, 14). In 1974 the FCA decided to focus on two issues: an income insurance system for all seniors and a national policy for the frail elderly (15). For the latter issue the Council established a Task Force on the Frail Elderly under the leadership of Monsignor Fahey. William G. Bell and Leonard Cain served as consultants to the frail elderly project.

The phrase, frail elderly, was not felt to have any "special originality" but "was selected because of the need for a dramatic term to focus attention on this very special grouping of the elderly" (15). The Task Force agreed that the characteristics of the frail elderly included "physical debilities … (and) emotional impairment, as well as debilitating physical and social environments" (15). Bertha Adkins, Chair of the FCA in 1976, stated that "these persons require continuing support from society because of an accumulation of the debilities of increasing age" (16). By 1978 the FCA defined the frail elderly as "persons, usually but not always, over the age of 75, who because of an accumulation of various continuing problems often require one or several supportive services in order to cope with daily life" (15). Basic or core services for the frail elderly subsequently identified by the FCA were assessment of need, development of a care plan, and case management. As an administrative device for "triggering" access to these core services, the FCA recommended using the age of 75 or greater (15). There was little initial reaction from the geriatric medical community in the United States to this work. What can be found was not positive; an article in *Geriatrics* responding to the recommendations of the FCA referred to "frail elderly" as an example of the jargon used by the Council (17).

Researchers began in the 1980s to explain what

they meant when they used the terms "frailty" or "frail elderly" in their papers. Early definitions for the "frail elderly" included: those aged 75 or greater; a vulnerable population of seniors because of physical or mental impairment; older individuals admitted to a geriatric program; those requiring institutional care; and seniors dependent on others for activities of daily living (ADLs) (18-23). Chronic diseases and their sequelae were felt to be the cause of functional limitations (21, 23-25). There appeared to be a growing consensus that frailty was another term for disability in older individuals. An example of this can be found in Robyn Stone's paper on caregivers of the frail elderly where she used "frail elderly" and "disabled older individuals" as interchangeable terms (26).

A number of concepts arose concurrently during this time that dealt with maintaining health and preventing frailty as we age. Loss of vigor, vitality, or resilience has long been considered an important feature of senescence (27-29). James F. Fries built on this prior work in his description of the "compression of morbidity" (30). Fries and a colleague, Lawrence M. Crapo, proposed what they termed a "new syllogism" for aging: 1) median natural human life span is fixed at around 85; 2) the age of first infirmity can be increased by effective preventive approaches; and 3) therefore the duration of infirmity will decrease (31). In support of this viewpoint was the observation that persons with better health habits (defined in terms of not smoking, having an appropriate body mass index, and/ or exercising) experienced less disability in their later years (32, 33). Several measures of disability in older age have shown improvements over the last decade in the United States (34). Fries recently argued that this provides empirical evidence of the actual occurrence of the compression of morbidity (35).

This hope that we can live a vigorous life and experience only a short pre-terminal period of disability is not new. It was expressed most poetically in Oliver Wendell Holmes' 19th century work "The Deacon's Masterpiece; or, The Wonderful 'One-Hoss Shay'". An expertly built carriage was described as remaining in perfect running order until it fell apart "All at once, and nothing first, -/ Just as bubbles do when they burst."

In recent years, increasing interest began being paid not only to the quantity of life but also its quality. Katz et al. defined "active life expectancy" as the expected remaining years of functional well-being, in terms of ADLs (36). Active life expectancy was found to be adversely influenced by both poverty and limited educational attainments (36, 37). A consistent finding has been a longer average duration of dependency in women as compared to men (36, 38-40). Extending active life expectancy has become a public health goal.

The initial use of frailty in reference to older individuals by the FCA was driven by a desire for a striking term in order to focus attention on a group of seniors with special needs. The FCA did not claim to be describing anything new. The term, though, developed a life of its own. In the 1990s definitions of frailty which did not depend on the presence of chronic diseases, dependency or need for health/social services began appearing. The stance that frailty was nearly synonymous with disability was perceived by many as inadequate. They felt that frailty had to be more than just disability. A number of difficult questions were asked. Were younger adults with disabilities frail? Were all older disabled patients frail? If not, why weren't they? Was a "pre-disabled" state of frailty present and identifiable? How did one end up frail? What was the underlying mechanism?

What drove the shift in emphasis from "being frail" to "becoming frail" is not entirely clear. Arguably it reflected the evolution of thinking on frailty and a desire for a more profound understanding of it. Once disability occurs, it may be too late to reverse the process. From the standpoint of trying to intervene, moving to a "pre-disability" stage would hold attractions. The need for geriatric programs to target older patients likely to be responsive to their intervention may have had an influence. As Nourhashemi noted, it "seems evident that targeted interventions would be more effective if they were initiated before the loss of autonomy" (41).

b) Frailty and specialized geriatric programs

The "frail elderly" were (and still are) often stated to be the appropriate target population for specialized geriatric programs (42-48). An important event in making this link between specialized geriatric programs and the frail elderly was the National Institutes of Health Consensus Development Conference on geriatric assessment methods (49). The Panel held that comprehensive geriatric assessment was particularly suited to the needs of the frail elderly. The frail elderly were described as patients who "exhibit great medical complexity and vulnerability; have illnesses with atypical and obscure presentations; suffer major cognitive, affective, and functional problems; are especially vulnerable to iatrogenesis; are often socially isolated and economically deprived; and are at high risk for premature or inappropriate institutionalization" (49).

Defining frail seniors by whether they are likely to benefit from an intervention (50), though, raises problems. It can become circular logic: as these programs are for frail seniors, those admitted must be frail. It may also lead to the exclusion of a subgroup of frail seniors because of program issues. In an effort to identify older frail hospitalized patients who might benefit from an interdisciplinary geriatric consultation, Winograd excluded 12% of admitted older patients as being too functionally impaired to benefit (51). Many would feel that this group is frail even though they may not be an appropriate target population for a geriatric program. In other words, the targeting needs for these programs may lead to the exclusion of some "frail" individuals because of the severity of their functional impairments.

Utilization of long-term care services has also been used to define frailty. For example, Brody et al. defined frail elders as being either judged nursing home eligible, requiring intensive long-term home-based care, or being admitted to a nursing home (52). Admission to the Program of All-inclusive Care for the Elderly (PACE), a program that provides community-based long-term care and medical services for patients eligible for nursing home placement, has been equated to being frail (53).

At best, these service-determined definitions function as a proxy for the actual condition of frailty. Criteria for admission to a program generally have some unavoidable vagueness in language making them open to interpretation, have a degree of built-in flexibility, and are open to "gaming" by the practitioner (54). Another concern would be the stability of the designation. For example, in an American study, being categorized as "nursing home certified" (NHC) was used as criteria for the presence of frailty (55). Among survivors, less than half (43%) remained NHC after one year.

c) Clinical presentations associated with frailty

In the early 1970s Bernard Isaacs put forth a concept which may represent the far extreme of the frailty spectrum (56). A retrospective review of all the deaths that occurred during 1968 in residents of Glasgow aged 65 and over was performed (57). A subsample was selected and detailed information on their final illness was obtained from relatives. Isaacs found that a high proportion of deaths in old age, especially in those 75 and older, was preceded by a period of prolonged dependency characterized by the loss of mobility (i.e., unable to walk without human support from bed to toilet), incontinence (i.e., frequent and persistent incontinence of either urine or stool), or cognitive impairment (i.e., so severe that the person could not function safely or independently). Isaacs called this "pre-death" where older persons "outlive the vigor of their bodies and the wisdom of their brains"; in other words "the survival of the unfittest" (57). He felt that there was an urgent need for research, education of providers, and re-organization of health services to cope with this "difficult period of life through which many of us will inevitably have to pass" (57). Notwithstanding this plea for investing in the study of causation and management, the term did not lead to a hopeful perspective. Pre-death seemed to be a stage of life which had to be endured, not prevented nor conquered.

Recent studies of the clinical profiles of older decedents re-visit the pre-death concept. In their first paper Lunney et al. used Medicare claims data to examine the clinical usefulness of a classification system for older decedents. They found that the commonest (47% of all decedents) trajectory at the end of life was what the investigators called "frailty" (58). Members of the frailty group showed steady, progressive decline before dying from complications associated with "advanced frailty". They were identified in this study by a Medicare claim during the last year of life associated with a diagnosis of stroke, Alzheimer's disease, dementia, delirium, Parkinson's disease, hip fracture, incontinence, pneumonia, dehydration, syncope, or lower extremity cellulitis. They next performed a cohort analysis using data from the Epidemiologic Studies of the Elderly (EPESE) longitudinal study (59). A fifth of decedents had a frail trajectory. They were significantly older than the other trajectory groups (sudden death, terminal illness, organ failure) and were more disabled throughout their last year of life.

Failure to thrive (FTT) in older persons has been at times equated with frailty. This syndrome was first described in the late 1980s (60). As initially framed, older patients with FTT were stated to be losing weight and declining both physically and mentally. Depressive features were also felt to be a core finding. Like pre-death, FTT was stated to occur near the end of life (61). Causation of FTT was held to be complex with both organic and non-organic factors potentially contributing. FTT has been criticized as reflecting both undue fatalism and intellectual laziness (62). As a diagnosis, it appears to have fallen out of favor. Another term for this presentation was "the dwindles" (63).

Disease presentations which have been called atypical (i.e., delirium, falls, immobility, incontinence, functional decline, breakdown of social sup-

ports) are commonly encountered in older patients and may occur preferentially in frail seniors (64, 65). Frail seniors also appear to be particularly susceptible to iatrogenesis. For example, their lack of physiological reserve is felt to predispose them to adverse drug effects (ADEs) (66). Pharmacokinetic concerns with frailty include changes in distribution volumes, lower levels of albumin and of plasma esterase activity, and declines in both creatinine clearance and hepatic metabolism of drugs (21, 67, 68). Marked variability in phenytoin serum concentrations has been found in frail nursing home patients (22, 69). The use of benzodiazepines is associated with urinary incontinence in frail older patients (70). Frailty has been stated to be a risk factor for severe ADEs (71).

In the next sections of this paper, we will be dealing with current thinking about frailty. There is not a sharp demarcation between historical and contemporary meanings of the term. As will be seen, the roots of some of our contemporary models go back a hundred years and more.

4) MODELS

The following models (as well as the definitions and criteria in subsequent sections) should not be viewed as mutually exclusive. There is duplication and overlap among them. Components within one may have intended or unintended relevance for another. At times different words are used for very similar concepts. While the diversity presented indicates the lack of consensus, it also speaks to the isolation of researchers working on frailty.

a) Demographic and mathematical

A mathematical model can be defined as a symbolic device utilizing mathematical reasoning that is built to simulate and predict aspects of the behavior of a system. Many biomedical and psychosocial researchers are more comfortable with verbal rather than mathematical models for complex phenomena. However, mathematical models do offer certain advantages. They force the researcher to articulate a clear understanding of the assumptions underlying their model. Their precise predictions make it easier to reject them if they turn out to be incorrect in contrast to verbal models, which make relatively imprecise predictions that are more difficult to refute. Working through the model can reveal non-obvious and surprising implications which merit further exploration. The success of any model, mathematical or otherwise, is determined by the extent that it allows us to explore, confirm, refute, refine, and revise our ideas.

Demographers have developed models for survival that include a factor for unobservable heterogeneity or "frailty" (72). In mortality modeling, frailty is a measure of general susceptibility to death (73). Hougaard described frailty as "a random effects model for time variables, where the random effect (frailty) has a multiplicative effect on the hazard" (74). The concept of frailty has been used to explore susceptibility to the aging process as a whole with the outcomes simplified to the states of "healthy", "disabled", and "deceased" (75). This susceptibility may reflect genetic predisposition or the cumulative effect of environmental exposures. Formal models with a frailty parameter predict that as mortality decreases, population frailty should increase (76). Though we are living in a time of declining mortality rates, there are no data indicating that increasing rates of frailty have actually occurred. In fact, there is evidence that the opposite might be happening (35).

A demographic observation is the deceleration of death rates at extremes of old age in a variety of populations including humans (77-79). One possible explanation for this is heterogeneity of frailty. Frail individuals are more likely to die leaving a select subset of robust survivors. This possible explanation is supported by data from the New England Centenarian Study (80, 81). Alternatively, if everyone is sufficiently frail, death may become primarily "accidental" due to pervasive but minor environmental stresses which exceed the reserves of the individual (79). The mortality plateau may occur because of slowing of the aging process at the level of the individual (79). The "reliability theory" predicts a late life mortality deceleration with subsequent leveling off and later-life mortality plateaus because of redundancy exhaustion at the extreme of old age (82). Other mathematical models to explain the mortality rate plateau in late life have been suggested (83).

Speechley used Principal Components Analysis to examine intercorrelations among characteristics and disabilities (84). Eighteen pre-selected factors were examined. Nine met criteria for frailty (age over 80, balance and gait abnormalities, infrequent walking for exercise, depressed, taking sedatives, decreased strength in shoulders, lower extremity disability, near vision loss) and four met criteria for vigor (age under 80, cognitively intact, frequent physical exercise other than walking, relatively good near vision). Subjects were considered frail if they had at least four of the frail attributes and no more than one vigorous attribute. The observed incidence of falling over one year of follow-up was

higher in the frail group (52%) compared to the vigorous group (17%).

Lipsitz has used "chaos theory" to explore frailty (85, 86). He suggested that the loss of complexity in a number of fractal-like structures and processes leads to "the loss of adaptive capacity and ultimate functional independence that characterizes frailty" (86).

Two recent publications show that a "frailty index" based on a count of accumulated deficits can predict the likelihood of mortality in populations of older individuals (87). In the first study, twenty diverse deficits were chosen while in the second study, 38 variables were considered (88). These deficits included symptoms/ signs (e.g., trouble with vision), impairments/ disabilities (e.g., need help to prepare meals), and general medical problems (e.g., hypertension). The authors speculate about an "avalanche-like destruction of the organism through the accumulation of defects" (88).

A more detailed review of some of the mathematical models has been published (89).

b) Aging

A simple model for frailty would be that it is intrinsic to aging. Fifty years ago Perlman described what he called the Aging Syndrome in terms akin to how frailty is now described (90). To quote, "Overtaxation of defense reserves and lowered target resistance of stressed, isolated, related and combined functional and/or organic units are intimately involved with aging" (90). More recently, Evans defined the process of aging as the loss of adaptability of the individual which leads to an age-associated rise in mortality and disability rates (91). This also is close to some of the current thinking about frailty. The precise role of increasing age in the etiology of frailty, though, remains unclear. It appears that while, on average, adults are more likely to be frail with increasing age, frailty as a state is not universally present in older persons. This suggests that frailty is associated with aging but it is not an inevitable consequence of the aging process.

Older individuals vary in their overall robustness (76). It has been suggested that frailty is synonymous with "accelerated aging" (92). Presumably accelerated (or pathological aging) can be distinguished from usual aging or successful aging (93). Both disease states and psychosocial factors are extrinsic factors that influence the pattern of aging. Current understanding of successful aging, though, does not necessarily equate it with an optimal level of over-all functioning and well-being. Very few at the extremes of old age met this exacting standard (94). Successful aging as viewed by older individuals is a process of adaptation (95).

c) Genetic

Frailty depends at least partially on genetic attributes (76). Studies on *Caenorhabditis elegans* (a popular animal model for the genetics of aging) suggest that higher mortality risk with aging occur because of homeostasis failure and destabilization of the genome (96).

With aging, there is cumulative damage to nuclear and mitochondrial DNA. This damage and its incomplete repair can lead to a reduction in fuel produced by cells and a decreased ability to build proteins (97, 98). The accumulation of "bioenergetically deficient cells" due to mitochondrial mutations might lead to a number of the core characteristics of frailty: muscle weakness, declining mental capacity, and diminished cardiac function (99). Genes that enhance stress resistance may be a major determinant of longevity and allow us to age with retained vitality (100, 101). The apolipoprotein E4 genotype might be a possible risk factor for frailty. A Danish study reported that E4 carriers had a relative risk of 1.13 (95% CI, 1.05-1.22) of dying between 40 and 100 compared to the E3/E3 or E4/E2 genotypes (102). Greater functional decline was found in older women with the E4 allele in another study (103).

It is very unlikely, though, that frailty arises solely from genetic factors. Even in the relatively simple animal model of *Caenorhabditis elegans*, stochastic (random, non-programmed) as well as genetic factors are felt to be important determinants of the manifestations of aging (104).

d) Primary pathways

Sarcopenia (the loss of muscle mass and strength with age) has been suggested as the major underlying cause of frailty (105-108). The loss of muscle mass and strength in older individuals is a common phenomenon with significant consequences. For example, a cross-sectional study found that sarcopenia was often present in older individuals (especially women) and was associated with a higher likelihood of functional impairment and disability (109). It is also found in animal models of aging. Gradual, progressive deterioration of muscle, resembling sarcopenia, can be observed with aging in *Caenorhabditis elegans* (104).

Sarcopenia arises from incompletely understood mechanisms (110, 111). Purported causes include loss of alpha motor neurons and muscle fibers (es-

pecially of fast-twitch fibers), decline in muscle cell contractility, impaired function of remaining muscle cells, somatic mutations, deficient locally produced insulin-like growth factor-1 (IGF-1), deficiency in circulating growth hormone and IGF-1, androgen and estrogen deficiency, and dysregulation of cytokine formation (108, 112-118). Another suggested mechanism is the oxidative shift in the plasma thiol/disulfide redox state (119, 120). This age-related shift appears to be mediated at least partially by a decreasing capacity to remove dietary cysteine from the oxidative environment of the blood (121). A recent study showed that when adjusted for the baseline arginine level, N-acetylcysteine significantly enhanced the response to physical exercise in frail older patients and led to a decline in tumor necrosis factor levels (122).

With aging, there is a decline in the functioning of a number of endocrine systems. This leads to the development of menopause/andropause, adrenopause, and somatopause (123). These hormonal deficiency states may contribute to frailty. The belief that some of the manifestations of aging arise from a hormonal deficiency has a long pedigree. In the late 19th century Brown-Sequard, then in his 70s, treated his declining endurance, strength, and mental abilities with a crude testicular extract that was derived from dogs and Guinea pigs (124). Recent work has focused on insulin-like signals. Suppression of insulin-like peptides, insulin-like growth factor, lipophilic signaling molecules, and sterols or their receptors can increase life span, delay age-related functional decline and increase stress resistance in nematode, insect, and mouse animal models of aging (125).

A low level of chronic inflammation secondary to age-related dysregulation of the immune system has also been proposed as the underlying cause of frailty (126-129). Increased levels of interleukin-6 (IL-6) and the acute phase reactant, C-reactive protein, have been found in frail seniors (130-132). Again, the history of this concept has its roots in the 19th century. Elie Metchnikoff felt that aging arose from auto-intoxication due to the products of colonic microbes. Cells weakened by the effects of these toxins would then be destroyed by macrophages (133, 134).

Nutritional deficits are frequently associated with frailty (135). It is not clear whether these deficits are the cause or frailty, its consequence, or both.

There are a number of potential serum markers for frailty, disability, or adverse outcomes in older patients. These include: low testosterone levels (136); low testosterone and/or high lutenizing hormone (LH) levels (137); low DHEA levels (138); higher morning cortisol/ DHEA sulfate ratio and diminished response to the dexamethasone suppression test (139); increased levels of C-reactive protein, factor VIII, and D dimer (132); high IL-6 levels (130); high IL-6 and/or D-dimer levels (129); high serum IL-6 levels and low hemoglobin (131); low total cholesterol (140); low serum albumin (141); higher plasma osmolality (142); and an unexplained mild normocytic anemia (143). Additional biomarkers have been suggested (144).

Models which state that frailty reflects dysfunction of a single organ system are arguably taking an excessively reductionist approach. By focusing unduly on one aspect of the condition, they may be missing the whole. As John Godfrey Saxe wrote in *The Blind Men and the Elephant*, "The disputants, I ween, / Rail on in utter ignorance/ Of what each other mean, / And prate about an Elephant/ Not one of them has seen!"

e) Concurrent dysfunction of multiple biological systems

A number of recent models have speculated that concurrent impairments in several biological systems lead to frailty. Severely impaired strength, balance, and endurance have been suggested as underlying frailty (145). Examples of models which require multisystem dysfunction are as follows:

- Frailty is a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure (146). The authors recommended assessment of musculoskeletal function (e.g., grip strength, chair stands), aerobic capacity (e.g., sub-maximal treadmill, six-minute walk), cognitive/integrative neurological function (e.g., Mini-Mental State Examination, static balance), and nutritional status (body mass index, arm muscle area).
- Fried and Walston have proposed a "cycle of frailty". Sarcopenia, neuroendocrine dysregulation, and immune dysfunction are the "physiologic triad" felt to underpin the syndrome. The cycle or downward spiral can be precipitated by a "trigger event" (147, 148). An example of a trigger event would be a hip fracture (149).
- Frailty is related to the pathophysiological effects of an altered metabolic balance, manifested by cytokine over-expression and hormonal decline. Frailty is seen as the midpoint between inde-

pendence and pre-death. Factors which make frailty more likely are: advanced age, allostatic load score, physical disability/functional decline/need for help with ADLs and IADLs/dependency, falls and injuries (especially hip fracture), polypharmacy, chronic diseases, cognitive decline, depression, health care utilization, and nutritional impairment (112). A recent study found that the combination of low IGF-1 and high IL-6 levels was associated with a high risk of death and disability in a cohort of older women (150).

- Precursor of functional decline which leads to recurrent hospitalization, institutionalization, and death. Morley et al. feel there are four major intrinsic factors that lead to frailty: sarcopenia and related metabolic pathogenic factors, atherosclerosis, cognitive impairment, and malnutrition (151).
- Disease, disuse and aging "per se" trigger a mechanism that exhausts the redundancy of muscular and nervous backup systems and, when the damage goes beyond the threshold of possible compensation, leads to a measurable decline in physical performance (48).

A common feature of all these models is the involvement of multiple biological systems in the pathogenesis of frailty. Deficits do not appear to arise in isolation (88). For example, there appears to be an association between physical and cognitive impairments. There is evidence that physically frail older individuals often have impairments on psychometric tests (152). Women with low fat-free soft tissue mass have been found to have a higher likelihood of cognitive impairment (153). Likewise, women who have rapid bone loss are more likely to show cognitive decline in the future (154). The possible mechanisms underlying this require exploration. It might be that these individuals have a higher rate of intrinsic aging or some other common process, such as inflammation, which leads to both physical and cognitive decline. An interesting recent observation is the regulation of brain amyloid concentrations by IGF-1 levels in an animal model (155). Deficiencies in growth hormone and IGF-I have been implicated in sarcopenia and frailty (114). Worse cardiorespiratory fitness has been found to predict greater cognitive decline in six years (156). Cardiorespiratory fitness may reduce the risk of specific medical conditions that are associated with impaired cognition, increase cerebral blood flow, and/or stimulate nerve cell growth.

Whether cognitive impairment should be included or excluded as one of the primary biological systems underpinning the development of frailty, though, remains an unsettled area. Campbell and Morley both feel that it should be included (146, 151). On the other hand, Fried excluded individuals suffering from dementia/ severe cognitive impairment in her studies (157). This was justified by saying that the clinical features of frailty could arise solely as a consequence of a dementia. Because of the stated need for the involvement of multiple biological systems to say that frailty truly exists, the presence of dementia could lead to "false positives". Other researchers have qualified what they are studying as "physical frailty", which indicates that cognitive impairment is not a core feature in their conceptualization of the entity (145, 158-161).

f) Life course

Some frailty models can be categorized as life course approaches (162). With a life course approach, there is an attempt to understand etiology by studying the long-term effects of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life on the risk of developing a disease, condition or state. Biological, behavioral and/or social pathways, operating over an individual's entire life course and across generations, are examined. An effort is made to understand the complex interrelationships between these biological, behavioral and social pathways. Exposures acting during specific critical periods can have lasting effects on the structure or function of organs, tissues and body systems. These effects are not dramatically modified by later events. Adaptations may initially mask structural deficits which may become evident later in life as the adaptations fail.

Allostatic load would be an example of a life course model where there is gradual accumulation of damage over time (162-166). Allostasis is the ability of the body to increase or decrease vital functions ("the ability to achieve stability through change"). Allostatic load is the "wear and tear" (or "use it and lose it") that occurs in an organism over time in the effort to maintain a steady state. It can be viewed as an evolution of older studies on the long-term effects of stress and the General Adaptation Syndrome of Seyle (167). For example, Perlman viewed "stressor-adaptive mechanisms" as important in understanding his Aging Syndrome (90). Allostatic load is a conceptualization of the cumulative biological burden exacted on the body through attempts to adapt to life's demands. A summary measure of allostatic load based on ten biological measures (four of which are primary me-

diators and six secondary mediators) was associated with poorer cognitive and physical functioning at baseline and in the future (163, 166).

An alternative life course model deals with disuse, uncoupling from the environment, and symmorphosis. Walter Bortz 2nd initially coined the term "Disuse Syndrome". It was developed to explain a number of the manifestations of aging (168, 169). He subsequently wrote two conceptual papers about frailty. In the first he speculated that frailty "results where the organism is uncoupled from its environment yielding a break in the forward feedback cycle of stimulus to reaction to growth to increased functional competence to improved response to stimulus" (170). A simplification of his premise is "use it or lose it." Bortz more recently has written about the relationship between frailty and the concept of "symmorphosis" (167, 171). Animals are designed economically. Symmorphosis postulates a quantitative match of design and function; it further holds that within a given pathway of sequential steps the capacities of each step tend to be matched. Rather than a rate limiting step, control is invested throughout all steps. Bortz holds that frailty arises from a "lessened load" on the person that "leads to linked and parallel losses in form and function". He further says that "Frailty is herein defined as a state of muscular weakness and other secondary widely distributed losses in function and structure that are usually initiated by decreased levels of physical activity" (167).

Allostatic load and symmorphosis are not mutually exclusive concepts. It is felt that there is an optimal balance between "use it and lose it" and "use it or lose it." Where that balance rests is uncertain. It is possibly dynamic, changing with time in a given individual (172). This idea of a necessary balance might be captured by the concept of hormesis, which is generally understood as beneficial effects with low doses of an otherwise harmful physical or chemical agent (173). A more scientific definition of hormesis is that it is an adaptive response characterized by biphasic dose-response relationships (174). A number of mild stresses (e.g., cold, heat, irradiation, and caloric restriction) have been found to induce increased longevity in various animal models (175). Hormesis might result from either direct stimulation or an overcompensatory response to a noxious stimulus (174). To prevent frailty it may be that the individual has to be exposed to a mild load or stress in order to induce the appropriate adaptive response. To quote Friedrich Nietzsche, "What does not destroy me, makes me stronger."

g) Combined biomedical/psychosocial

There have been attempts to develop frailty models that recognize diverse contributing factors operating on a number of levels (molecules to societies). Examples of these combined models include:

- Frailty occurs when an older patient has problems in more than one of the following dimensions: medical (known illnesses, drugs being taken, significant past medical history), functional (self-care, mental competence), social (support network, finances, social isolation, loneliness), and psychosocial/psychological (premorbid psychological traits, expectations of aging, inactivity, invalidism, fear) (176). Brook stated that the more dimensions affected, the frailer the patient would be but also wrote, "severe problems in any one dimension can, in itself, define a frail older person" (176). While diverse contributing factors to frailty were noted, this early model lacked precision. The dimensions noted were very similar to the elements typically included within comprehensive geriatric assessment (49).
- Building on the "model of breakdown" of Brocklehurst, the dynamic model of frailty recognizes a complex interplay of assets and deficits for a given individual (177). Assets (health, functional capacity, positive attitude, caregiver, and other resources) are those things that help a person to maintain independence in the community. Deficits (chronic disease, disability, dependency, and caregiver burden) threaten independence. Frail individuals are those where the deficits outweigh the assets ("frail elderly in institutions") or where they are in a precarious balance ("frail but still live in the community") (178). This model by Rockwood et al. was tested by examining factors associated with institutionalization of older people (179). Female sex, being unmarried, absence of a caregiver, cognitive impairment, functional impairment, diabetes mellitus, stroke, and Parkinson's disease were all independently associated with institutionalization. These findings were felt to support the contention that frailty was not just disability but rather represented a "multidimensional construct" (179). In turn, the multifaceted nature of frailty in this model was felt to support the "nature of comprehensive geriatric assessment, providing another rationale for assessing functional, medical, psychosocial, and environmental data" (179).
- Frailty is conceived by Kaufman (180) as both a quality (arising from objective criteria) and as a dynamic adaptive process on the part of

the older person, families, and health care personnel. "It comes into focus at the moment when any combination of an old person's symptoms and behaviors is construed to tip the balance towards a problem of more dependence than independence with regard to functional ability and social role performance" (180).

- Another dynamic model was proposed by Lebel et al. (181). Predisposing factors influence the development of age-associated changes and diseases which in turn can cause impairments. Cognitive, neuro-locomotor, and energy metabolism (which includes cardiopulmonary capacity and nutritional status) impairments are emphasized in the model. Functional limitations and disability evolve from the impairments. The impact of these biological and clinical events is modulated by the personal, social, environmental, and health system resources that can be mobilized. This model was seemingly influenced by the description of the disablement process (182).

All of the above models emphasize the dynamic nature of the interplay between the various contributing factors. How seniors adapt to the deficits seen with frailty is an unexplored area. The SOC (Selection-Optimization-Compensation) Model is a pro-active strategy for age-related adaptation that consists of identifying goals (Selection), concentrating on developing the abilities needed to achieve these goals (Optimization), and selecting alternative approaches when losses occur (Compensation) (183). An alternative strategy would be reactive; you would cope with losses by being flexible with your aspirations and adjusting them (184). Which, if any, adaptive approach is preferred in the setting of frailty is currently unknown.

Much of the literature on frailty focuses on biological and medical factors. There has been a tendency to view social factors as being of secondary importance - either modifiers of the primary biological processes leading to frailty or characteristics which influence the impact of frailty on the older person (181, 185-187). This may be excessively restricted. Recent work suggests that social factors such as social support and degree of engagement are associated with disability levels (188, 189). Some social gerontologists argue against the use of the term frailty and view it as a form of negative stereotyping (190, 191). Frailty is not a term that older patients use when talking about themselves (190).

Another component, which has not been studied as extensively as biological systems, is the environment. Successful task performance is dependent on a match between task demands and capabilities (192). Functional independence in frail older persons might be maintained by changing their environment so that the demands placed on the individual will be congruent with their abilities (193).

5) DEFINITIONS

Most definitions proposed for frailty are nominalistic (194). With nominalism the purpose of the definition is to state the features by which the entity can be recognized. The meaning of the concept is made clear by using other concepts which have been already adequately defined. The following definitions may go no further than the recognition of a familiar pattern or may include a discussion of underlying causes.

a) Dependency

Some frailty definitions focus on the presence of dependency. Examples of these definitions are as follows:

- The frail elderly are those older persons who, because of some degree of disability, are in need of some assistance (195).
- Those more than 65 years of age who are dependent on others for ADLs and are often institutionalized (24, 196).
- Old debilitated individuals who cannot survive without substantial help from others (197).
- Those who have deficits in ADLs and require the help of others (198).
- Chronic limitation in ADLs or instrumental ADLs (199).
- Physical frailty has been defined as impairments in physical abilities needed to live independently (158). Physical frailty so defined was considered the sole cause of disability in 40% of persons living at home with limitations in ADLs. Mental or sensory impairments (with or without physical frailty) led to the other 60%.
- Frail elderly people comprise those over the age of 65 with one or more functional, cognitive or social impairments (200).
- Chronically dependent older people with a variety of physical and/or cognitive impairments that impede daily functioning (201).
- Functional losses that may interfere with the ability to maintain autonomy in everyday life (190).
- Diminished ability to carry out the important practical ADLs (IADL, going out into community, having hobbies and activities, and walking to keep active) and social ADLs (interacting with family, friends or acquaintances on a consistent basis, providing and receiving support) (202, 203).

- Institutionalization as defined by entry into a nursing home or chronic care hospital for the purpose of long-term care (179). While the vast majority of institutionalized seniors were felt to be frail, the authors recognized that not all frail older people were in institutional care; in other words, this definition would be specific but not very sensitive.
- Meet criteria for nursing home placement (53).

The path from a state of functional well-being to disability for an individual has received intensive study over the last twenty years. The International Classification of Impairments, Disabilities, and Handicaps of the World Health Organization and its revision were important steps forward (204, 205). The elaboration of the disablement process has provided additional insights that have informed a number of the models developed for understanding frailty (181, 182, 206-208). Concepts such as main pathway, risk factors, extra-individual factors, and intra-individual factors can be found in a number of the frailty models.

The work by Stuck et al. in identifying risk factors for functional status decline highlights a number of similarities between the risk factors for disability and frailty (209). Stuck found that strong risk factors for a decline in function included depression, no alcohol consumption or heavy alcohol consumption, cognitive impairment, co-morbidity, reduced lower extremity performance (e.g., chair stands), high BMI or low BMI or weight loss, low physical activity, poor self-rated health, smoking, low frequency of social contacts, and poor vision (209). Strawbridge et al. found very similar predictors of frailty - depression, heavy drinking, prevalence of chronic symptoms/chronic conditions (co-morbidity), fair or poor self-rated health, smoking, physical inactivity, and social isolation (210).

Relatively little work has been done on understanding how disability develops over time. Two general patterns have been described: catastrophic (sudden) and progressive (211-213). Progressive loss becomes more common with increasing age and in the presence of multiple co-morbidities (213). Progressive development of disability is the more common pattern seen with frailty (48, 53, 58, 59, 211).

A challenge for dependency-based definitions is explaining how frailty differs from disability. What is the value-added in using the term frailty? Current thinking appears to be moving towards thinking of frailty as a "preclinical state of disability" (214). Frailty here is viewed as one of the pathways to disability. The other pathways would be the direct effects of diseases and environmental barriers.

b) Vulnerability

Most of the current definitions emphasize vulnerability to decline and/or other adverse outcomes.

- Loss of physiological reserves by older people which deprives them of a margin of safety (215).
- An inherent vulnerability to challenge from the environment (216).
- An overall loss of physiological reserves, feebleness and general vulnerability (76).
- Frail elderly are older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or other infirmity (217).
- Individuals lacking in strength who are delicately constituted or fragile. A state of reduced physiologic reserve associated with increased susceptibility to disability (186).
- Physical frailty is the result of accumulated losses within physiological systems resulting in reduced function and intolerance to challenge (159).
- Grouping of problems and losses of capability that make individuals more vulnerable to environmental challenge (210). A frail person is someone with deficiencies in more than one area or domain of functioning (i.e., physical, nutritive, cognitive functioning, and sensory problems).
- Increased vulnerability to insults or challenges resulting from impairments in multiple domains that compromise compensatory abilities (65).
- Frailty is the loss of functional homeostasis (218), i.e., the ability of an individual to withstand illness without functional loss.
- Frail older persons were defined as subjects lacking in general strength and who are unusually susceptible to disease and other infirmities (219).
- Risk that older individuals have of developing or worsening either functional limitations or disabilities, given the combined effects of deficiencies and modulating factors (181). This definition emphasizes the dynamic and progressive nature of frailty.
- Inability to regain function after an acute illness (220).
- A combination of deficits or conditions that arise with increasing age and contribute to making the elderly person more vulnerable to changes in the surroundings and to stress (41).
- A biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (157).

- Inability to withstand acute illness or emotional upheaval or physical dislocation (221).
- Vulnerable older people are persons 65 years of age and older who are at increased risk of functional decline or death over two years (222). Those with frailty are at the highest risk of decline or death.
- Frailty is characterized by high degree of susceptibility to external and internal changes that require adaptation or compensation (144). Frail patients have a high risk of homeostasis disruption and consequent development of negative health outcomes, including disability and death.
- An intermediate stage in which the individual experiences heightened vulnerability to medical, psychosocial, or environmental stressors (223).
- Frailty is a pathologic condition that results in a constellation of signs and symptoms and is characterized by high susceptibility, impending decline in physical function and high risk of death (48).

Though the concept of frailty as vulnerability is becoming generally accepted, there are a number of unresolved questions. Is vulnerability any different than prior thinking (29, 224) about age-associated deterioration in homeostasis and homeodynamics? This deterioration with age has been called defective homeostasis, homeostenosis, impaired homeostasis, loss of functional homeostasis, integrative decline, and homeostatic balance failure syndrome (66, 218, 225-229). The decline is felt to underlie senescence which has been defined as the progressive loss of resilience with age, even in the absence of accidents and disease (29). With senescence "sudden perturbations, easily accommodated by a homeodynamically resilient organism, are debilitating or lethal" (29). This wording is very similar to a number of the definitions proposed for frailty. If we state that frailty is different in some fashion, how is it different? Possibly one difference is that we may be looking at the interaction of multiple organ systems which are concurrently deteriorating. A second distinction from prior thinking about declining homeostasis might be the emphasis on adverse outcomes other than death.

Vulnerability is present to a degree in all of us. As noted, "An unalterable given in human existence is the possibility of injury and destruction, the quality of frailty" (230). Many authors have noted a spectrum spanning fitness to frailty (84, 100, 202, 231, 232). When is the threshold crossed and the person becomes frail? In the future will we be able to accurately measure frailty as we currently measure biological attributes like blood pressure? Unfortunately, at present the determination of the older patient's vulnerability may only occur *post-hoc,* after the older persons have demonstrated their vulnerability by not overcoming the challenge they faced.

c) Disease states

The presence of medical conditions has been used to define frailty. Examples of this approach include:

- Elderly with chronic conditions (25).
- The presence of any single medical condition that is characterized as serious or restricting (233).
- Presence of co-morbidities (71).

Most current thinking on the relationship between diseases and frailty is that diseases - like cardiovascular conditions (234) - can contribute to the occurrence of frailty or worsen its severity. Prevention aimed at certain diseases might decrease the likelihood of frailty arising. Medical condition(s) may function as a marker for frailty or its likely development. For example, incident urinary incontinence in older individuals is associated with a higher risk of physical impairments and functional limitations (235). At advanced ages the importance of disease states in leading to disability declines (236). Whether this is also true for frailty is unknown.

6) CRITERIA

The general definition of frailty in the Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) trial was "severely impaired strength, mobility, balance, and endurance" (237). A pre-planned meta-analysis of cross-sectional data from the FICSIT trail found that gait velocity (walking at usual pace over 3-40 m), balance function (ability to maintain balance for at least 10 seconds in parallel, semi-tandem, and tandem stance), chair rise times (standard chair with arms crossed over chest; time required to stand) and grip strength (dynamometer, right hand) were independently related to IADL deficits after correcting for covariates (age, sex, years of schooling, MMSE score, Falls Efficacy score) (238). These and other simple physical measures such as functional reach (159) have been looked at as a means of identifying frailty and/or the risk of future adverse health outcomes. The ones that have attracted the most attention are lower and upper extremity performance measures and the assessment of nutritional status.

Tests of lower extremity function such as walking speed and results of a short battery of physical

performance tests (standing balance, timed walk, timed repetitions standing/sitting) have been found to be predictive of future disability (239, 240). Outdoor mobility, indoor mobility, walking speed, and knee extension strength were predictive of mortality (241). Diminished maximal isometric knee extension strength before a fracture predicted mortality after it occurred (242). The adjusted relative risk of dying for those in the lowest tertile was 4.4 compared to the highest tertile. Problems with one-leg standing balance have been proposed as a marker that might be helpful in screening for frailty (243, 244). Many seniors, though, may be unable to perform even relatively simple physical performance measures of the lower extremities (245).

Tests of upper extremity function have also been found to be associated with future disability and death. Diminished hand grip strength has been stated to predict incident disability (246, 247). Giampaoli et al. found that in men the incidence of disability over the next four years increased with decreasing strength from 25.6% in the highest quartile to 48.3% in the lowest quartile (246). In the Honolulu Heart Program the risk of functional limitations and disability in men 25 years later increased as baseline grip strength declined (247). The odds ratio of having a walking speed of 0.4 m/s or slower was 2.77 in the lowest tertile compared to the highest. The odds ratio for being unable to rise from a chair was 2.73. The risk of a self-care disability was more than 2 times greater in the lowest *vs* the highest tertile. Lower grip strength has been found to be associated with a higher mortality risk (241).

Even modest weight loss is associated with a higher risk of mortality in older subjects (248). Unintentional weight loss has been associated with poor self-rated health and long-standing disability in aging men (249). Weight stability within an acceptable range seems to be associated with the lowest mortality (250). A BMI of less than 23 compared to one of 23 or greater has been found to be associated with a higher risk of death (18 *vs* 5%), disability (IADL dependency; 40 *vs* 20%), and cognitive decline (drop in MMSE score; 22 *vs* 7%) over 5 years (251).

Detecting attributes of frailty has been proposed as a way to identify frail seniors. Some, but not all, of these attributes are physical performance measures. Specific criteria that have been suggested for either identifying current or predicting future frailty include (listed in chronological order):

- Hospitalized patients aged 65 years of age and older who have any one of the following: cerebrovascular accident; chronic and disabling disease; confusion; dependence in ADLs; depression; falls; impaired mobility; incontinence; malnutrition; polypharmacy; pressure sore; prolonged bed rest; restraints; sensory impairment; socioeconomic/family problems (44). Patients were excluded if they were independent or severely impaired. Being categorized as frail was associated with a number of adverse outcomes. Compared to the independent group, those who were categorized as frail had a longer average length of stay in hospital. Over the next year the frail group was more likely to be admitted to a nursing home (34 *vs* 3%) or die (45 *vs* 13%). These criteria were utilized to identify frailty in a recent randomized, controlled trial of exercise and vitamin D that showed no beneficial effect of the interventions (252). In this latter study, potential subjects were excluded if, in the opinion of the responsible clinician, treatment was potentially hazardous or definitely indicated. Other exclusionary criteria included a poor prognosis (i.e., unlikely to survive 6 months), severe cognitive impairment (i.e., Mini-Mental State Examination score of less than 20), physical limitations that would limit adherence to the exercise program, unstable cardiac problems, large ankle ulcers, non-fluent English, and residence outside the hospitals' catchment area.
- In an attempt to look at the prevalence of frailty, three criteria for frailty were compared: dependence in ADL (using the Katz ADL scale); ADL dependence or poor self-rated health or dementia; and ADL or instrumental ADL dependence (253). The prevalence of frailty for the three definitions ranged from 19 to 41%.
- A 7-item screening instrument to identify frailty was developed for older patients admitted to hospital (254). Questions dealt with cognitive ability (unable to give year, name days of the week forward and backward), mobility (need assistance getting to the bathroom), emotion/ nutrition (loss 6 or more pounds in the past year), diagnosis/ treatment (taking 4 or more medications, hospitalized overnight within previous 30 days), and age (age over 85). A positive response to any of these questions would make the patient high risk. The screening instrument was evaluated in the emergency department of a community hospital over a 3-month period. Participants had to be over 75 years of age, living at home, and requiring hospitalization. Most (86%) participants had a positive response to at least one of the items.

- Research subjects in an intervention study were felt to be physically frail if they were 70 years of age or older and were residents of a facility providing long-term care (160). They had to be able to walk 6 m, and subjects would be excluded if they had severe cognitive impairment, rapidly progressive or terminal illness, acute illness or unstable chronic illness, myocardial infarction, fracture of a lower extremity within 6 months of the trial, or insulin-dependent diabetes. They were also excluded if they were on a weight-reducing diet, undergoing resistance training at the time of enrolment, or if the baseline assessment revealed a musculoskeletal or cardiovascular abnormality.
- A pre-morbid (2 weeks before hospital admission) Barthel Index (BI) score of less than 95 defined frailty in a study of hospitalized older patients (64). Compared to "well" seniors, frail seniors were older, more likely female, and not living in the community. Frail seniors were more likely to have an atypical or mixed illness presentation (59 *vs* 25%). During their stay in hospital, the frail group was more likely to have an adverse outcome (length of stay greater than 30 days, failure to return to within 10 points of the pre-morbid BI by discharge, new admission to a long-term care facility, death).
- The Hospital Admission Risk Profile (HARP) was designed to identify older patients at high risk for developing new disabilities following admission for an acute medical problem (255). Results are based on a 5-point scoring system. Points are assigned for age (<75 = 0; 75-84 = 1; 85+ = 2), score on an abbreviated MMSE (15-21 = 0; 0-14 = 1), and IADL function prior to admission (independent for 6-7 = 0; 0-5 = 2). A score of 4-5 is high, 2-3 intermediate, and 0-1 low risk. The rates for ADL decline at discharge were 55, 31, and 19% for the high, intermediate, and low risk groups in the validation cohort. At three months, the figures were 37, 19, and 9%. Patients had to be 70 years of age or greater and were hospitalized in one of six hospitals. Exclusion criteria included terminal illness, severe cognitive impairment, inability to give informed consent, and admission to the intensive care unit. Additional exclusion criteria included being admitted for surgery, living in a nursing home before admission, dying during the hospitalization, or dying within 3 months of discharge.
- Four self-reported variables (age, presence of health conditions that interfere with daily activities, needing or receiving assistance from another person for bathing, or for taking medications) were evaluated as a way to predict the development of frailty (defined as being nursing eligible, requiring admission to a nursing home, or needing intensive home care assistance) over the next year (52). The sensitivity of the variables in predicting subsequent frailty was 50.7% with a specificity of 97.8%.
- Hospitalization for any of the following seven conditions: pneumonia (including aspiration pneumonia), urinary tract infection, cellulitis/abscess of the leg, septicemia, dehydration, syncope, and hip fracture (256). As can be seen, the first four conditions are infectious diseases and the latter two are associated with falls.
- Hospitalized seniors who experience a decrease in their overall functional level (pre-illness *vs* discharge from hospital) of at least one point on the Functional Independence Measure instrument (218). Those who showed a functional decline when compared to those who did not, had a higher 6-month readmission rate (59.4 *vs* 39.7%) and a higher rate of an adverse outcome (78.1 *vs* 50%).
- Subjects with World Health Organization Assessment of Functional Capacity (WHOAFC) scores of 21 or more and a self-report of fair or poor health were stated to be frail. A score of 20 or less on the WHOAFC suggests that the person can perform all or most basic and instrumental ADLs independently. If the two measures did not agree, the subject was categorized as frail or not based on their self-rated health (257). In a small study (N=84), postural sway with eyes closed with a moving surface and dorsiflexion strength were significant predictors of the frail state. Subjects had to be 60 years of age or older, living independently in the community, able to speak and read English, and have sufficient vision to read large print. Exclusion criteria included a diagnosis of a neurological disease, arthritis with severe pain that prevented activity or presence of symptoms of cardiopulmonary or metabolic diseases unless physician approval was obtained.
- Frailty was assessed by asking older individuals about 16 variables grouped into four functional domains (210). Four items assessed problems with physical functioning (sudden loss of balance, weakness in arms, weakness in legs, get dizzy or faint when standing up quick-

ly); two, nutritive functioning (loss of appetite, unexplained weight loss); four, cognitive functioning (difficulty paying attention, trouble finding the right word, difficulty remembering things, forgetting where put something); and six dealt with sensory problems (vision - difficulty reading a newspaper, recognizing a friend across the street, or reading signs at night; hearing - difficulty hearing over the phone, hearing a normal conversation, or hearing a conversation in a noisy room). Scoring for the six sensory items was 1 (no difficulty), 2 (little difficulty), 3 (some difficulty), and 4 (great deal of difficulty). For the other items, scoring was 1 (never or rarely over the last 12 months), 2 (sometimes), 2 (often), and 4 (very often). Subjects scoring 3 or higher on at least one item in any domain were considered to have a problem in it. Participants were classified as frail if they had problems in two or more domains. Of the 574 subjects, 26.1% were frail. Frailty rates increased with increasing age and were marginally higher in males. They were lower among those with 12 years or more of education.

- Chin A Paw et al. compared three working definitions for frailty in older men (258). All definitions required physical inactivity (defined as less than 210 minutes per week of physical activity). This would then be combined with energy intake less than 7.6 MJ per day (if non-prescribed), a 5-year weight loss of more than 4 kg, or a BMI of less than 23.5. Inactivity/weight loss was associated with more baseline abnormalities and a greater likelihood of death, an increase in disabilities, or a decline in performance measures over three years. They concluded that inactivity with weight loss seemed a suitable working definition for frailty. This Dutch study was limited to males living independently.
- Rockwood et al. described a "Frailty Scale" (231). Older individuals had their mobility, self-care, bladder control, and cognition assessed. They were then classified on a 4-level scale: 0 (walk without help; independent for ADLs [eating, dressing, bathing, bed transfers]; continent of bowel and bladder; and not cognitively impaired); 1 (bladder incontinence only); 2 (one, two if incontinent, or more of needing help with mobility; needing help with self-care; incontinence; or having cognitive impairment); and 3 (two, three if incontinent, or more of total dependency for transfers; one or more of ADLs; incontinence of bowel and bladder; and diagnosis of dementia). The frailty scale showed a dose-response relationship between grades of frailty and subsequent institutionalization and death. The scale was based on the Geriatric Status Scale which was developed to identify hospitalized older patients appropriate for a geriatric consultation (259).
- Gill et al. examined how baseline vulnerability and precipitating hospital events contributed to the development of dependency (260). Predisposing factors were gait speed (time to walk 10-foot course: 10 or less seconds, >10 seconds), Mini-Mental State Examination score (<24 or 24 and greater), and age (85 and over, <85). Using these three characteristics, subjects were categorized as low, intermediate, or high risk for functional decline. Precipitants were hospitalizations; certain lengths of stay, diagnoses, or procedures increased the magnitude of the precipitating events. The outcome of interest was the development of a new disability in one or more of 7 ADLs at the one-year interview or admission to a skilled nursing home prior to the one-year follow-up. A double-gradient phenomenon was found with both baseline risk and precipitating events contributing to the risk for new functional dependency.
- Ershler stated that frailty is characterized by decreased bone mineral density, reduced lean body mass, decreased serum cholesterol and albumin levels, increased inflammatory mediators, and mild to moderate anemia (126, 261).
- Rolfson et al. developed a "Frail Scale" that incorporates 10 items: cognition (Clock Drawing Test), hospital utilization (number of admissions to hospital in last year), self-rated health, instrumental ADLs, availability of social support, medication use (5+ on a regular basis, non-adherence), nutrition (weight loss), mood (depression), continence, and mobility ("get up and go" test). It is intended to detect older individuals at risk for functional decline and who might benefit from the involvement of specialized geriatric services. It reportedly takes five minutes to administer (262). Content validity was stated to be excellent.
- For an interventional study, frailty was defined as any of the following: concern about community living; recent bereavement, hospitalization, or acute illness; frequent physician contact; multiple medical problems; polypharmacy; adverse drug events; functional impairment or functional decline; and diagnostic uncertainty (263). These criteria were used in a study of specialized geriatric care for rural se-

niors. The intervention did not prolong life or delay institutionalization but those in the intervention group were more likely to attain treatment goals.

- Saliba et al. (222) developed a scale that included age (1 point for 75-84; 3 points for 85+), self-rated health (1 point for fair or poor), physical activity (6 items asked about; 1 point if only with a lot of difficulty/unable up to a maximum of 2), and instrumental ADLs/walking across a room (5 items; 4 points for any with difficulty). A score of 3 or greater identified what the authors called a vulnerable group. The scale was developed on a nationally representative sample of 6205 Medicare beneficiaries. Those with a score of 3+ were 4.2 times as likely to die or show functional decline over two years. The ROC had an area of 0.78. Adding self-reported diagnoses did not substantively improve the predictive ability of the scale.
- Scores on the 36-point modified Physical Performance Test (PPT): not frail 32-36; mildly frail 25-31; moderately frail 17-24 (232, 264). There are nine standardized tasks in the modified PPT. Seven are timed: 50-foot floor walk (25 feet out and back); put on and take off a laboratory coat; pick up a penny from the floor; stand up five times from a 16-inch chair; lift a seven-pound book from waist level to a shelf overhead; climb one flight of stairs; stand with feet in side-by-side, semi-tandem, and tandem positions (eyes open). There are two additional non-timed tasks (climb up and down four flights of stairs, and perform a 360 degree turn). Each item is scored 0 to 4. The group of investigators later added to the modified PPT in their criteria for mild to moderate frailty. Subjects had to have at least two of the following: modified PPT score between 18 and 32; peak oxygen uptake between 10 and 18 mL/kg/min; self-reported difficulty or assistance with one basic ADL or two instrumental ADL (265).
- Fried et al. (157) have proposed that the presence of three or more of the following describe the frailty phenotype: muscle weakness (grip strength in the dominant hand in the bottom 20%), exhaustion/fatigue (positive response to "I cannot get going" and "I feel that everything that I do is an effort"), less physically active (bottom 20% for kilocalories expended per week), slow/ unsteady gait (bottom 20% for height and sex adjusted range for walking 15 feet), weight loss (unintentional loss of 4.5 kg in the previous year). Data from the Cardiovascular Health Study (CHS) was used to test the criteria. The CHS is a prospective, observational study of men and women 65 years of age and greater (N=5888). Exclusion criteria included history of Parkinson's disease, Mini-Mental State Examination score less than 18, receiving L-dopa/donepezil/or antidepressants, receiving active therapy for a malignancy, being wheelchair-bound in the home, likelihood of moving out of the recruitment area within the next 3 years, and being unable to come in for a baseline assessment. Over three years, those categorized as frail were more likely to have fallen, experienced worsening mobility or ADL function, been hospitalized or to die. Unlike the other criteria reviewed in this section, these are said to identify the frailty phenotype. Phenotypes describe the visible properties that are produced by the interaction of genotype and environment. It would be premature at this time to conclude that these criteria truly describe the frailty phenotype.
- Imuta et al. (266) modified the Japanese Ministry of Health and Welfare criteria for evaluating dependency to operationally define frailty. A self-administered instrument was used. Older individuals were asked to rate their degree of disability. If they rated themselves as being "mostly independent in daily living activities at home, but cannot go out without assistance", they were classified as frail. This study was conducted in two cities in northeast Japan. Participants were randomly selected. Entry criteria included living in the community and being 65 years of age or greater.
- Various operational definitions were to be compared in the study by McDowell et al. (267). One definition was being partially or totally dependent on one or more ADLs; a second categorized patients as frail if they were dependent for one or more ADLs, showed cognitive problems (3MS score of less than 78), or had a poor self-rated health. The third definition looked at the balance between deficits (2+ health problems, 1+ ADL impairment, 1+ IADL impairment, 3MS score <78) and assets (available caregiver, >12 years of education, "excellent" self-rated health). A total of 8% of males and 14.8% of females met the ADL definition.
- In a small cross-sectional study (N=78), Ho et al. built (268) on the work of Strawbridge to identify

older subjects at high risk for frailty. Participants were volunteers who responded to newspaper articles directed at older individuals. Those consenting to the study were asked 16 questions broken into five domains: physical functioning; nutritive functioning; cognitive functioning; vision problems; and hearing problems. Those who reported difficulty in more than one domain were classified at high risk for frailty. Those at high risk for frailty were more likely to report a decline in their physical activity; they also reported more physician visits and medications. Results of the study showed that high risk individuals did worse on many performance measures (i.e., timed "up and go", obstacle path, angular path, tandem balance, tandem gait, unimanual coordination, timed ADLs, scratch test, sit-and-reach).

- Individuals 65+ receiving long-term home help services (homemaking, personal care, and/or food preparation) who were judged to be at high nutritional risk (either involuntary weight loss of >5%/ last month, >7.5%/ 3 months, >10%/ 6 months + BMI <27 or BMI <24) (269).
- Gill et al. (161) in a randomized controlled trial of a home-based exercise program used the following criteria to define physical frailty: more than 10 seconds required to perform a rapid gait test and/or inability to stand up from a seated position in a hardback chair with arms folded. Those meeting one of the criteria were considered moderately frail; those meeting both were considered severely frail. Those in the experimental arm showed less functional decline during the study. Subjects were excluded if they were unable to walk, were receiving physiotherapy or participating in an exercise program, did not speak English, had a diagnosis of dementia or scored less than 20 on the MMSE, had a life expectancy of less than 12 months, or had suffered a stroke, myocardial infarction, hip fracture, or had undergone a knee or hip replacement within the previous 6 months.
- Patients who were 70 years of age or older, used a care service, and had a self-reported BMI of 25 or less or noted involuntary weight loss were enrolled into an intervention study for frail seniors (270). Potential subjects would be excluded if they were participating regularly in physical activity of moderate to high intensity, had been taking multivitamins for the previous month, were institutionalized, suffered from a terminal illness or had a rapidly deteriorating health status, and could not understand the study.
- Female patients aged 75 years or older, hospitalized for an acute illness who had difficulties in mobility and balance when admitted (271). Exclusion criteria included severe heart or circulatory disease, severe dementia, acute skeletal fracture, malignant terminal illness, and inability to walk.
- A measure of instability in health based on the Minimum Data Set 2.0 called the Minimum Data Set – Changes in Health, End-stage disease and Symptoms and Signs (MDS-CHESS) has been suggested as a way to identify frail seniors in long-term care settings (223). A 6-point (0-5) scale consisting of a count of health symptoms (0, 1, or 2 for a count of vomiting, dehydration, leaving 25% of food uneaten, weight loss, shortness of breath, and edema; more than 2 symptoms were counted as 2), nurse rating of a deterioration in cognition (1 point if present), nurse rating of a decline in ADL (1 point), and the presence of end-stage disease (1 point) was developed. In chronic hospital patients, the MDS-CHESS score predicted death over nearly 3 years. This is an interesting effort in that many would feel that nearly all institutionalized seniors are frail.
- Carvalhaes-Neto et al. defined those with frailty as being institutionalized seniors whose MMSE score was 20 or lower and had difficulties in 4 or more ADLs (139).
- Physical inactivity (defined as lowest tertile on an activity scale) alone or in combination with weight loss (6.3% of baseline weight over 4-5 years) predicted more chronic diseases, lower self-rated health, worse physical performance, and more disabilities (272). This group also required more health services and was more likely to have markers of impaired nutrition. Participants had to be living independently (non-institutionalized).

The thirty criteria noted above were developed for differing purposes and used on various populations. Notwithstanding this, the above criteria do meet, at least partially, the requirement for content validity though concerns about comprehensiveness persist. They by and large do have face or clinical credibility. Because of the lack of consensus on what frailty is, we do not have a "gold standard" that can be used for evaluating their validity. A number of the criteria used in non-interventional studies have been examined for their ability to anticipate subject outcomes over the next year or longer (e.g., 44, 52, 157, 222, 231, 258). Rigorous construct

validation has not been attempted to date for most of the criteria listed nor has an assessment of their respective reliability (273).

7) IMAGERY

Just as aging is often symbolized as a rising and falling staircase (274), various images have been used to represent frailty.

The favored figure for the representation of how frailty and/or disability arise is an algorithm (see Fig. 1 for a simplified version of the typical format). These outline the intervening steps leading to frailty. Most are unidirectional with few, if any, feedback loops identified (147, 148, 151, 170). A primary pathway (or pathways) starting from "ultimate causes" is delineated. Modifiers of the primary pathway are shown on occasion (182, 186). Adverse outcomes arising from frailty may also be indicated. Algorithms have been used to describe specific aspects of frailty such as how it impacts patients and caregivers (187). Cycles and spirals (Fig. 2) are an evolution of algorithms that emphasize the reinforcing nature of the key components that underlie frailty (147, 148, 157, 164, 181, 214).

Another commonly used pictorial are plots (Fig. 3) where some attribute (e.g., reserve, physiological capacity, physical capacity, level of function) is graphed against age (147, 158). Typically a threshold line is shown, below which a person would be judged as frail (147, 148). Ebrahim (193) included an interesting modification: she showed a lowering of the threshold by an environmental modification indicating the possibility of reducing the consequences of a decline in physical capacity.

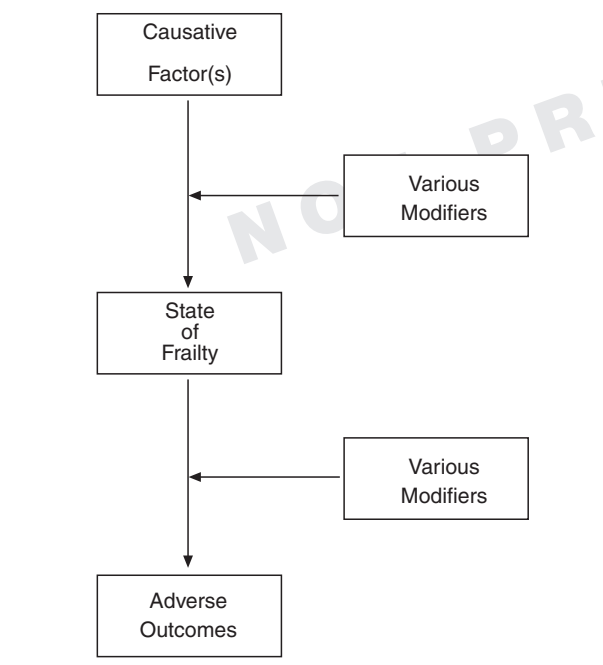

Figure 1 - *Algorithms.*

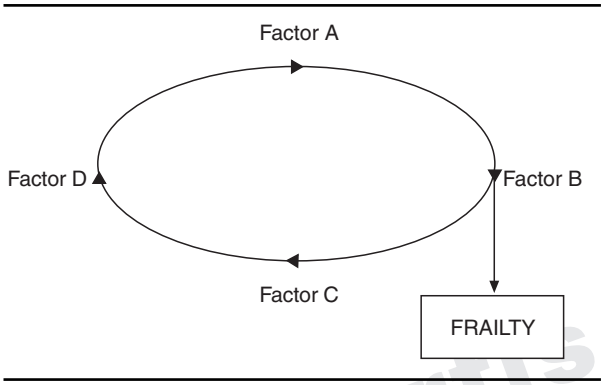

Figure 2 - *Cycles.*

A balance beam (Fig. 4) has been used to describe frailty (178). This representation does emphasize that the process is dynamic with the possibility of reversibility. Fried et al. did produce a Venn diagram displaying the overlap of frailty, disability, and co-morbidity (157). Bortz used a bar diagram to show the relationship between percentage of maximum function and disability, frailty, profound functional loss or death (167).

8) CONCLUSIONS

A large array of models, definitions, and criteria has been proposed for frailty. At the present time there is no universally accepted understanding of frailty. Different terms are used for similar concepts. One is struck by a Tower of Babel quality of recent writings on frailty. "But God confounded their tongue, so that they did not understand one another's speech, and thus scattered them from their places into all lands, and they ceased to build the city" (Genesis 11:1-9). We must try to bridge the isolation of researchers by promoting the integration of concepts across diverse disciplines. Notwithstanding the uncertainty about what frailty actually means, a recent multidisciplinary survey found that most practitioners (69%) feel the term is clinically useful (275).

A recent review stated that models and/or defini-

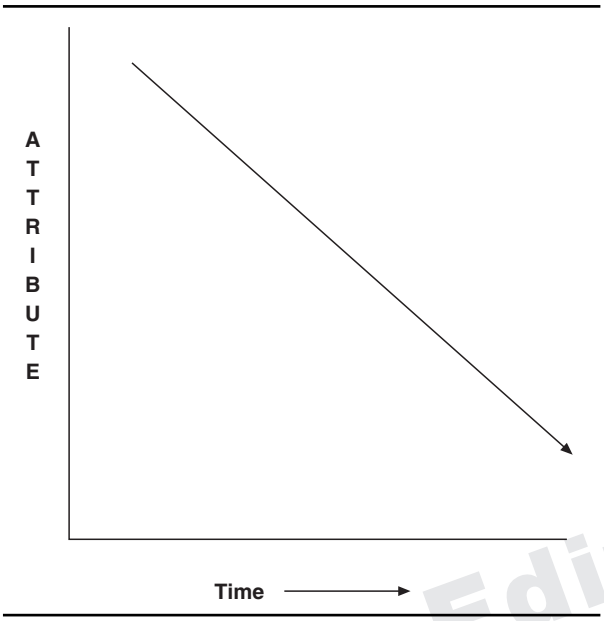

Figure 3 - *Plots.*

tions of frailty should include the following key components: the presence of multisystem impairment; instability; change over time; an allowance for heterogeneity within the older population; an association with aging; and an association with an increased risk for adverse outcomes (276). In addition, we would advocate an integrative and comprehensive approach which would include biological, clinical (including cognition), psychological, social, and environmental components which interact across a person's life span, delaying or promoting the emergence of frailty. This is at some variance with recent research that has in the main focused on "physical frailty".

Though initially viewed as synonymous with disability, most would now agree that frailty is not the same as having co-morbidities, impairments, disabilities, or handicaps. That is not to say these attributes are irrelevant to current thinking about frailty. Co-morbidities are felt to be an important etiological factor whereas functional limitations are manifestations of the state. While frailty is more common with increasing years, it is linked more closely to vigor and robustness rather than chronological age. There is an emerging consensus that it is primarily a state of vulnerability to experiencing adverse outcomes. The two approaches (disability and vulnerability) are not incompatible. Atchley wrote that, "As a concept, frailty refers to physical or mental weakness, fragility, and vulnerability. Frail people may seem as if their bones would easily break; their physical reserve capacity may be extremely limited, their mental processes may be confused or slow, and it would not take much to make them disabled. Indeed, many frail people are disabled" (277).

There is a need to develop a framework for frailty that is relevant for both clinicians and researchers. According to scientific realism, the object of study exists in the empirical (tangible) world while models or theories belong to the conceptual world of ideas. If we accept this perspective, we have to connect the two worlds. Definitions of theoretical concepts can serve as the bridge between the two. Data can be used to test the validity of the models by both examining the accuracy of their predictions and determining whether important findings were missed.

The various operational definitions or criteria proposed for frailty should be examined. To what models or definitions do they correspond? How do they compare in identifying frail seniors? Their validity, reliability, sensitivity to change, and practicality have to be examined and contrasted. Those which best withstand rigorous scrutiny should be advocated for both research and clinical practice.

The Canadian Initiative on Frailty and Aging will perform a systematic literature review. Areas to be covered include: biological and social basis of frailty (mechanisms, determinants/risk factors, markers throughout the life course, and their interaction); current and future prevalence and incidence (in various population groupings and settings using various definitions); natural history; impact on the individual, family, and society; identification and measurement; prevention and management; implications for health/social services; and health and so-

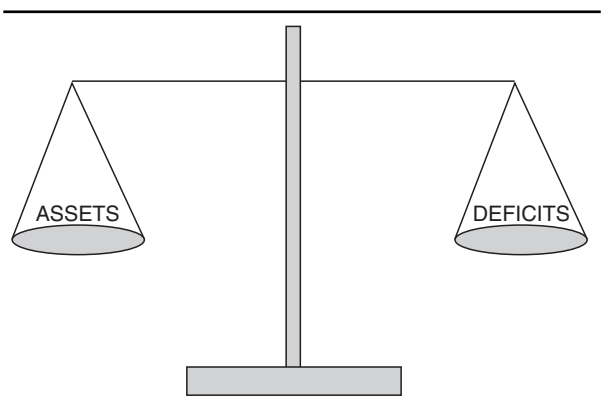

Figure 4 - *Balance beam.*

cial policy implications. The objectives are to collate and critically review what we know now, develop a research agenda, and develop a consensus on a framework for frailty. This in turn would lead to relevant practice and policy guidelines for health care professionals and decision-makers. This paper is just the first step in the process.

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