Editorial

The Top 10 Hot Topics in Aging

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I enjoy talking with very old people. They have gone before us on a road by which we, too, may have to travel, and I think we do well to learn from them what it is like.

—Socrates, in Plato’s The Republic

Each year in January, I have tried to review the cutting edge of geriatrics over the previous 2 years (1,2). This review is based to some extent on the high impact articles in the literature (3,4), but also on emerging areas. The Journals of Gerontology Series A also continue to welcome articles from some of our distinguished colleagues who have gone before us on the exploration of the wonders of aging and remain active contributors to the field of gerontology (5–8). This year, being my last year as editor of the Journal of Gerontology: Medical Sciences, I have decided to list what I believe are the top 10 hot areas in geriatrics.

Cognitive Decline

There is no question that finding solutions to cognitive decline and the behavioral problems associated with it is a central area in geriatrics (9–11). Our knowledge of the pathophysiology of Alzheimer’s disease is moving forward rapidly. While beta-amyloid has taken center stage, both as a neurotransmitter that produces learning and memory disturbances (12,13) as well as an initiator of tissue destruction, possibly through free radical activation (14,15), there is also increasing understanding of the tauopathies (16). A recent article showed that measuring tau protein in lip epithelial tissue could possibly be used to diagnose Alzheimer’s disease (17).

There is an increasing awareness of the importance in early recognition of mild cognitive impairment (18,19). Acute illness causes not only short-term but also long-term functional decline in persons with preexisting cognitive impairment (20). In particular, it is now becoming clear that cognitive decline is associated with a decline in physical performance (19,21–27). This is in part due to the decrease in reaction time associated with central nervous system damage (22). Cognitive dysfunction, whatever the cause, is associated with a high rate of medical comorbidity (23,28) and earlier mortality (24,29). The effects on mortality are worsened when cognitive dysfunction coexists with depression (29).

Over the last decade, there has been much enthusiasm for the possibility that hormone replacement therapy may improve cognition and slow progression of Alzheimer’s disease (30–33). However, the Women’s Health Initiative (WHI) in older women showed that hormone replacement therapy resulted in both a greater degree of cognitive dysfunction and an increase in the incidence of Alzheimer’s disease (34,35). At the same time, as these results have become known, there is an increasing belief that testosterone in males may improve cognitive function (36–38). A relationship between elevated homocysteine and vitamin B12 and folate deficiency with Alzheimer’s disease has been found (30,39). Other studies have suggested that hypercholesterolemia may play a key role in the development of Alzheimer’s disease and worsening cognitive function (40,41). Centenarians with high HDL (high-density lipoprotein) levels have better cognitive function and exceptional longevity (42). It is possible that cholesterol-lowering, especially in mid-life, results in a decline in atherothrombotic brain infarction, which may, in itself, be a causative agent for Alzheimer’s disease (43–46).

In the arena of treatment for Alzheimer’s disease, data continue to emerge that cholinesterase inhibitors slow the progression of the disease (9). Memantine, a drug that modulates the glutamate/NMDA system, can now be added to our therapeutic armamentarium and may prove useful either alone or in combination with cholinesterase inhibitors (47). Studies continue to appear that gingko biloba is a useful therapeutic adjuvant for persons with Alzheimer’s disease (48). The effects of gingko appear to be equivalent to some of the more mainstream therapeutic agents (49). There is an urgent need for high-quality, large (i.e., sufficiently well powered) studies utilizing this agent. An exciting recent study has shown that aerobic fitness reduces brain tissue loss in humans (50). Resistance exercise has recently been shown to improve function in people with dementia (51). These findings strongly reinforce the calls in the Journals to continue to exercise throughout life and maintain healthy lifestyle habits in order to compress morbidity (52–55).

While antibodies to beta-amyloid can reverse cognitive dysfunction in mice (48,49), the human immunization studies led to disastrous consequences, with some of the patients developing an inflammatory disease of the central nervous system (56). Thus, while we await the potential of antisense to beta-amyloid that can switch off its production...
or drugs that can inhibit the function of the amyloid precursor protein cleavage enzymes (secretases) (10,57,58), most of the care of patients with Alzheimer’s disease still need to focus on end-of-life care (59). As has been demonstrated by Simmons and colleagues (60), feeding the older demented patient takes an inordinately long time. New methods need to be developed to accurately quantify the amount of food consumed by older patients (61). Protein energy malnutrition can cause a marked decline in quality of life in nursing homes (62). Small changes in the emotional status of institutionalized elders can markedly alter food intake (63,64). Innovative programs such as the “Eden” alternative or even mechanical pet therapy need to be put in place to improve quality of care in nursing homes (65–68). As so eloquently suggested by John Schnelle (69), we need to “capture the voice of cognitively impaired elders” to improve their quality of life. Kane and colleagues (70) have provided one approach to doing this. Kane (71) has also called for professionals who have the experience of having loved ones cared for in long-term care facilities to band together in an attempt to find new solutions that will improve the quality of care in institutions. Volcier (11) has provided great insight into the management of behavioral systems in the demented person. It is important to realize that behavioral management and appropriate attention to the caregiver’s needs are far more powerful tools than the use of drugs to deal with behavioral problems. The recent explosion of the use of expensive antipsychotics, any of which have no proven efficacy, to treat behavioral problems in nursing homes is particularly to be deplored!

Finally, there is an increased awareness of the problems associated with driving in older cognitively impaired individuals and the need to more fully develop adequate transportation systems (72,73). Richardson and colleagues (74) have highlighted the importance of visual attention in maintaining driving skills. Global positioning devices are emerging as the best way to test true driving skills in older persons (75). Given the horrendous accident that occurred in California when an older person drove into a group of persons (76). A clearly emerging area is the use of taste enhancers (110) and giving caloric supplements between meals rather than with the meal (111). A clearly emerging area is the use of orexigenics to stimulate appetite (77,112). It has a smaller orexigenic effect than does megestrol. For centuries, cannabis has been known to create the desire to eat (117). Recently dronabinol, a pure tetrahydrocannabinol, has become available as an orexigenic. Yeh and colleagues (91), and cognitive processing time (96). Habitual walking has been shown to decrease the onset of physical disability in older persons (97).

**Depression**

An excellent review by Dan Blazer has summarized that state of the art for the management of depression (77). Depression remains underrecognized and undertreated in older persons, highlighting the need for continued screening (51,53,63,78). Physicians need to be made more aware of the effectiveness of treatment for depression. This is particularly important, as depression is associated with worse outcomes following a myocardial infarction, in persons with diabetes or congestive heart failure, or in those undergoing rehabilitation (55,77,79). Persons with depression are more likely to fall (80,81). Depression is also associated with increased mortality (29). The good outcomes seen with electroconvulsive therapy, particularly when bipolar electrodes are used, needs to be more widely advertised among physicians and the elderly population. In addition, resistance exercise has been shown to be an excellent adjuvant therapy for depression (82).

**Mobility**

The importance of mobility as an emerging area in geriatrics was highlighted by the fact that a single issue of the *Journals* was devoted to this topic (83–88). Lan and colleagues (89) have developed an objective index of mobility-related limitation. Walking speed is becoming recognized as an excellent measure of function. The ability to walk rapidly over a distance involves not only muscle strength (90–92), but also the integration of cardiovascular fitness (86), vision (93), postural stability (94,95), pain (91), and cognitive processing time (96). Habitual walking has been shown to decrease the onset of physical disability in older persons (97).

**Nutrition**

Undernutrition continues to be demonstrated to be a major factor associated with mortality in older persons (98). DeCastro (99) has painstakingly demonstrated the changes in eating behavior that occur with aging, including the decreased snacking between meals, that lead to the physiological anorexia of aging (100,101). Abnormal eating behaviors such as dietary restriction occur commonly in older women (102), but only in the minority of cases do they lead to disease processes such as recurrence of anorexia nervosa or anorexia tardive (103). The physiological factors involved in the pathophysiology of this aging-related anorexia have been recently reviewed in the *Journals* (95,104). Ghrelin, a hormone that stimulates eating and releases growth hormone, is emerging as a potentially important hormone in the regulation of feeding behavior. It is released from the stomach in response to fasting. Studies so far in older humans have shown no change or a small decrease with aging (105,106). PYY (3-36), another gut hormone, has been shown to inhibit feeding in humans (107) and cause weight loss in mice (108). To date, however, the best evidence for the early satiation that occurs in older persons implicates cholecystokinin (109).

New approaches to the management of weight loss in older persons have included using taste enhancers (110) and giving caloric supplements between meals rather than with the meal (111). A clearly emerging area is the use of orexigenics to stimulate appetite (112,113). Yeh and colleagues (114) have shown in a controlled trial that megestrol acetate produces weight gain in malnourished older persons. Its effect appears to be mainly due to inhibition of cytokines. The orexigenic effect of megestrol has been confirmed in other studies (115). Megestrol, however, does decrease testosterone levels in males (116). Thus, in males, when it is used, consideration should be given to giving testosterone at the same time. Females have better weight gain than males when they are given megestrol. For centuries, cannabis has been known to create the desire to eat (117). Recently dronabinol, a pure tetrahydrocannabinol, has become available as an orexigenic. It has a smaller orexigenic effect than does megestrol. Its ideal use is most probably in the palliative care arena, where, not only does it increase food intake, but it also...
decreases pain and nausea and improves mood. There is a need for large studies to determine the utility of orexigenic agents in the treatment of undernutrition.

Unfortunately, little attention is being paid to the role of vitamin and trace element deficiency in the pathogenesis of functional impairment in older persons. Certainly, they can play an important role in delirium; now that the yellow intravenous multivitamin (“banana bag”) mix is widely available again, consideration should be given to its use in older hospitalized patients. Urinary incontinence is a major reason for institutionalization in older persons (118,119). Vitamin B₁₂ deficiency has been associated with the development of incontinence (120). Zinc deficiency is extremely common, especially in older diabetics (121,122). It is associated with anorexia, immune dysfunction, and poor wound-healing. More studies are needed on the role of zinc deficiency in chronically ill elderly individuals. Creatine supplementation enhances isometric strength when utilized together with resistance training in older adults (123).

While inadequate attention is paid to undernutrition and vitamin and mineral deficiency, a large amount of research is actively exploring the role of dietary restriction as a means to extend life span. Bodkin and colleagues (124) have suggested, from early studies in dietary-restricted rhesus monkeys, that this approach may decrease mortality and morbidity. Banks and colleagues (125), in studying Ethiopian baboons over the life span, suggested that dietary restriction really represents prevention of obesity, as baboons in the wild have minimal fat stores as measured by leptin. While dietary restriction does not appear to prevent central nervous system damage (126), it certainly decreases glycation in nonhuman primates (127) and improves beta-cell sensitivity (128). Banks and colleagues (129) found that some garbage-eating baboons in Kenya developed the metabolic (insulin resistance) syndrome. Their studies strongly suggested that the environment interacts with the genome to produce this syndrome, as not all the baboons were affected. In the human studies in Biosphere 2, caloric restriction appeared to have a number of potentially beneficial effects (130).

**The Hormonal Fountain of Youth**

The WHI has created great disarray among the adherents to the concept that hormonal replacement will reverse the stigmata of aging. While the WHI did not show that estrogen/progestagen replacement increased mortality, it did show an increase in breast cancer, heart disease, and pulmonary embolism (131,132). This was offset by a decrease in colon cancer and hip fracture. This enormously expensive study was stopped prematurely based on a convoluted formula for early stoppage of the trial, thus leaving room for doubt about whether long-term hormone replacement therapy would increase or decrease mortality. In addition, as already alluded to, the study showed worsening cognitive function in the women receiving hormones (34,35). The estrogen-alone arm of this study continues and may help give further insight into these conundrums. Progesterone clearly increases the propensity to form thrombi and may also have played a major role in the pathogenesis of breast carcinogenesis. The women in this study were older, and thus the study provided little guidelines for the appropriate use of hormonal replacement therapy at the time of the menopause. However, it would seem clear that women in their sixties and beyond should not receive combination hormonal therapy.

In males, the enthusiasm for testosterone replacement continues unabated, but is based on a relatively small body of evidence-based medicine (36,133–135). A number of studies on testosterone replacement in older males have appeared in the *Journals* (136–139). Overall, testosterone in older men appears to be a quality-of-life drug improving libido (134) and the ability to obtain an erection when phosphodiesterease inhibitors are taken (140), as well as increasing muscle mass and possibly strength (141), and bone mineral density (142,143), while decreasing body fat (136). The effects of testosterone on cognition are controversial (36,138,141,142,144,145). Testosterone clearly increases hematocrit in older men. The effects of testosterone on prostate cancer carcinogenesis are controversial (36,133). The need for a large men’s health study to determine the efficacy and safety of testosterone in older males should be a national imperative. The intriguing hypothesis of Bhasin and colleagues (146) that testosterone plays a role in determining the fate of mesenchymal pluripotent stem cells may hold a major key to understanding the aging process. The role of testosterone in the development of frailty in older women is also coming of age (147).

While data suggesting that growth hormone and insulin-growth factor-1 may play a role in maintaining muscle mass (144,148,149), the enthusiasm for the use of growth hormone in the aged appears to be ebbing (150,151). One publication did, however, suggest that, in a single large family, growth hormone dwarfs had a shorter life span than their normal-sized siblings (152). This would appear to be in contradiction to animals where growth hormone deficiency confers longevity (153,154).

The role of vitamin D beyond its importance in maintaining bone mineral density remains controversial. There is a suggestion that it may play a role in preventing disability in older persons (155). There is, however, evidence that physicians continue to fail to diagnose and treat osteoporosis in older persons (156,157).

**Frailty/Sarcopenia**

As originally highlighted by Fried and colleagues (158) in the *Journals*, frailty is becoming a highly important geriatric syndrome. Frailty appears to be an important precursor of disability and functional decline (which in themselves are key predictors of mortality in older persons) (159,160–162). The causes of frailty are multiple and include not only alterations in muscle function, but also cognitive impairment and a decline in VO₂ max (163,164). Diseases such as diabetes and cardiovascular disease are clearly important in accelerating the onset of the frailty syndrome (165–169). Pain can increase the level of disability (170). As older adults are already performing their activities of daily living at close to maximum capacity, a small change can tip them over into the realm of disability (171). Exercise, particularly resistance exercise, appears to be the major weapon in
the therapeutic armamentarium to reverse frailty and its consequences (172–181). Falls are a sentinel event that can cause a frail person to transition to disability and functional impairment (182). Fear of falling in frequent fallers can lead to further disability (183). The American Geriatrics Society guidelines represent an excellent approach to the management of falls (184).

**Cardiovascular Disease**

Cardiovascular disease is present in over half of the older population and an even greater number of nursing home residents (195). The *Journals* has continued to carry a number of review articles to keep its readers abreast of the rapid developments in this field (196–200). Many of these have been written by Bill Aronow, a true geriatric giant who ages extraordinarily successfully as one of the most productive geriatricians, at an age when most have retired, and as a highly competitive tennis player. As an iconoclast who hates to embrace new expensive therapy, feels it incumbent upon him to point out the growing evidence of the superiority of angiotensin receptor blockers for the treatment of hypertension and heart failure (201–203).

The management of hypertension in older persons, and particularly the old-old is one full of opinions and still short on evidence (197,204). To highlight this area, James Goodwin (205) wrote an excellent review article, which was subject to a careful dissection by a variety of commentators (206–214). It is this kind of discourse that forces us to carefully examine the true state of evidence-based medicine in the older person. It is very important that geriatricians do not fall into the trap of considering trials conducted in middle-aged persons or even the young old as being appropriate to guide aggressive therapy in our unique population.

Finally, when treating hypertension in older persons, it is important to remember that white coat hypertension, pseudohypertension, orthostasis, and postprandial hypertension occur commonly. Orthostasis and postprandial hypertension occur more commonly in the morning than later in the day (215,216). Postprandial hypertension appears to be due to the release of vasodilatory peptides, such as calcitonin gene-related peptide (217).

**Immune Systems and Aging**

The deterioration of the immune system with aging is well recognized (218,219). The development of protein energy malnutrition can further cause deterioration in the immune system, resulting in a decrease in CD4+ T cells (220). Both nutritional supplementation and exercise have been demonstrated to boost the immune system (154,221–223); older persons appear to be particularly susceptible to anthrax when used as a tool of bioterrorism (222). As might be expected, older persons have worse outcomes when exposed to some of the new infectious disease outbreaks such as West Nile Virus (224) and SARS (225). Transfusion-related West Nile virus is more common in older than in younger persons (224). This reminds us all of the importance of vaccination against influenza in our older population (226,227).

**“The Merchants of Immortality”**

From the start of human history, alchemists have attempted to prolong the human lifespan (228). The extension of life remains an appropriate area of research for gerontologists, though we should continuously be on guard for science that extends longevity without compressing morality, as was the case for Tithonus, the morning lover of the goddess of dawn, Aurora. The appropriate approach to antiaging research has been the subject of a number of commentaries in the *Journals* (229–233). A particularly aggressive area of longevity research is to study the factors that distinguish the successful old-old, especially centenarians, from the rest of the population in the hope of unlocking the genetic keys of longevity (234–241). This area has been closely linked to similar research in animals (242,243).

The mechanisms of cellular senescence, as originally shown by Leonard Hayflick, remain an important area of immortality research (244–246). It was these studies that led initially to the search for telomerase (247). Originally thought to hold the secrets to cellular mortality, this area is now more of one in which researchers are hoping to treat cancer by controlling the enzyme. Hayflick’s original studies are also the basis for modern embryonic stem cell research an area that offers promise for tissue rejuvenation (248).

The ethics of longevity research, particularly in an era of capitalistic ownership of the “useful” human genes, is clearly a slippery slope. However, it should be recognized that, while the well-meaning argue how to move forward appropriately, those who are driven by fewer misgivings will likely not be deterred, allowing this area to be controlled by those who perhaps we would prefer did not hold the secrets to our future.

**Systems in Geriatrics**

Kane (249) has argued that geriatrics is at the crossroads and that to some extent we have failed, and we should remove ourselves from the mainstream and become the physicians for chronic care hospitals. This viewpoint was hotly contested by a variety of gerontological experts (250–259).

While geriatrics has not always delivered at the level I think many of us who entered the field in the 1980s hoped for, it certainly has changed the face of modern medicine. My colleagues and I have previously argued that a major role of geriatricians and our health care colleagues is to develop and run systems that decrease errors and improve care for elderly patients (260–262). This argument was based on the pioneering work of Larry Rubenstein on the value of Geriatric Evaluation and Management Units (263), whose value has been clearly confirmed (264,265). The importance for the installation of effective Continuous Quality Improvement systems to prevent errors is no longer in doubt (266,267). The addition of a high-quality computerized medical record to such a system will further enhance care (268).
Since the introduction of the geriatric evaluation and management unit concept, geriatrics has provided a number of other innovative projects that improve patient outcomes, e.g., Acute Care For the Elderly Units (ACE) (269), Delirium Intensive Care Units (270), Subacute Care Units (271), a geriatric-friendly nurse in the emergency department (272), and Program of All-Inclusive Care for the Elderly (PACE) (273), we have recognized the importance of controlling the rampant polypharmacy created by our other subspecialty colleagues (274). We have shown the ability of early screening to detect treatable geriatric problems (275,276). The geriatric Glidepaths have been created to help primary care physicians provide appropriate care to the wide range of older persons they encounter in practice (277). While our colleagues and administrators have been slow to incorporate these systems, they are slowly penetrating the high-technological environment of modern medicine. None of these systems function without well-trained geriatricians at their helm.

CONCLUSION

The future of geriatrics would appear to be more exciting at this moment than any time in the past. To conclude this editorial, I would, however, like to look back into our past, because where we are today in geriatrics is reflective of the small steps of the giants who created modern American geriatrics. This year, David Solomon celebrated his 80th birthday and was appropriately honored by a special supplement of the Journal of the American Geriatrics Society (278–282). David, together with John Beck, created the “West Coast geriatrics culture.” While extraordinarily different men in both personality and interest, David and John are truly the giants of modern geriatrics following in the footsteps of Bob Butler’s extraordinary achievement on the East Coast. I would like to add my happy birthday wishes to David and thank both David and John, not only for the inspiration they were to me, but also for their leadership in the gerontological world that I hold so close to my heart.

REFERENCES


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