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Editorial

Drugs, Aging, and the Future

DRUGS represent one of the classical conundrums of life: "We can't live with them; we can't live without them." It is now well established that older persons often receive excessive numbers of drugs that are often responsible for a variety of negative effects (1–3). Nancy Reagan's "Just say no to drugs" campaign may have produced more results if it had been aimed at seniors instead of teenagers! In many cases behavioral modification may reduce the need for drugs. Thus, distraction techniques can successfully reduce pain (4), and resistance exercise has been shown to reduce depression (5).

Besides the potential side effects of drugs, their high costs represent a major problem for many of our older patients. The drug companies argue that these costs are needed to recoup the costs of research and development. This is a rather shaky argument when one realizes that in the United States, pharmaceutical sales rose from $22 billion in 1980 to $149 billion in 2000. Only two of the top 13 pharmaceutical companies reported a loss in 2000. Merck reported a $6.8 billion profit with a 17% profit both on revenues and assets. Roche group reported a 30% profit on revenues, and Bristol-Myers Squibb reported profits at 27% of revenues. Overall, the pharmaceutical industry reported a 17% profit on both revenues and assets in 2000. In the Fortune global 500, big pharmaceutical companies accounted for six of the top 20 companies with highest returns on both revenues and assets. The AmEx Drug Index has consistently outperformed the Dow Jones Index in the last 5 years. There clearly is gold in them "thar" drugs!

Recently, experience has taught us that new, more expensive drugs are not necessarily better, but different. Nonsteroidal antiinflammatory drugs not only decrease pain but improve function (6). Thus, celecoxib, a cyclooxygenase 2 inhibitor, was shown to be equivalent to Naprosyn, a nonspecific cyclooxygenase inhibitor, in older persons in analgesic relief and in functional improvement (7,8). The occurrence of side effects was equal but different. Naprosyn caused gastrointestinal bleeding; celecoxib caused renal failure. Studies such as this clearly suggest that the FDA should require drug testing in persons over 75 years of age before approval. In addition, before a "me too" drug makes it to the market, it should have to show a statistical advantage in a head-to-head comparison with the drug on the market.

Physicians need to learn to prescribe drugs in a more rational manner. The Veterans Administration computerized medical record has revolutionalized the potential to decrease medication errors, as have programs such as ePocrates for the new generation of hand-held computers. We need to learn more about how physicians prescribe drugs to older persons, as shown in recent articles in the *Journal* on the management of gastroesophageal reflux disease (9), the use of cardiac medicines following discharge from hospital (10), the use of antidepressants (11), and the use of digitalis (12). Computer programs providing cost-effective, evidence-based management approaches to common outpatient diseases such as hypertension (13), congestive heart failure (14), diabetes mellitus (15–17), and hypercholesterolemia (18,19) should be available for our hand-held computers.

Despite this litany of problems with drugs, clearly drugs have played an important role in increasing the longevity of the aging population and improving their quality of life. Furthermore, future drug development has the potential to revolutionalize the management of the older person. The decline in functional performance that occurs with age (20–22) is clearly not reversible by nonpharmaceutical interventions, such as exercise, alone (23–25). This is not to belittle the importance of exercise and other lifestyle modifications in improving quality of life in older persons (26–30).

One of the areas in which we are liable to see major advances in drug therapy is in genomic manipulation. True gene therapy is just emerging from the stage of science fiction with the recent advances in stem cell research, animal cloning, transgenic animals, and gene knockouts. In contrast, biogenetically manufactured drugs have become a part of mainstream medicine.

Alzheimer's disease remains one of the major scourges of old age. The drugs presently available, although efficacious, produce minimal improvements for the majority of patients. However, the future appears to be very promising, with animal studies demonstrating that not only antibodies to beta-amyloid (31,32) but also antisense to amyloid precursor protein (33,34) can block beta-amyloid production and reverse cognitive dysfunction. These antisense molecules have been shown to cross the blood/brain barrier, making them potentially useful peripherally administered drugs (35). An area where new drugs may show dramatic effects is in the management of mild cognitive impairment (36).

Another area of potentially exciting drug development is in sarcopenia (37–40). The muscle loss with aging can clearly be attenuated with appropriate resistance exercise programs (41,42). However, many older persons fail to exercise, and exercise does not completely reverse this loss of muscle mass and strength. Myostatin is a protein that inhibits muscle growth (28). High levels are associated with muscle wasting. The development of myostatin inhibitors represents a potentially exciting area in the treatment of sarcopenia and cachexia.

There has been much enthusiasm for the use of growth hormone to increase muscle mass and strength. Unfortunately, the studies in animals and humans have been disappointing, with side effects outweighing positive effects (43,44). On the other hand, epidemiological studies have suggested that the testosterone decline that occurs with aging (45) may be the key factor in the decline in muscle mass and strength in older persons (46). Some testosterone replacement studies have shown an in-

crease in muscle mass and strength (47–49), whereas others have not (50). The enthusiasm to use testosterone in older persons has been tempered by the potential side effects such as elevated hematocrit and its effects on prostate cancer (51). Just as selective estrogen receptor molecules such as raloxifene have been developed for estrogen in an attempt to avoid its side effects, we can expect to see selective testosterone receptor agents developed (52). As was pointed out by Katz in a recent issue of the *Journal* (53), most of the testosterone effects on bone are mediated after it has been aromatized to estrogen. Kenny and colleagues (50,54) have shown not only that the decline of bone mineral density in aging men is related to the decline in bioavailable testosterone, but that testosterone replacement retards bone loss in older men. The availability of new forms of testosterone, such as the gel and hopefully a nontoxic oral form in the United States, should lead to rapid advances in our understanding of the role of testosterone therapy in older men. Of particular interest is the response of muscles to combination hormonal therapy as demonstrated in the article by Christmas and colleagues in this issue of the *Journal* (55).

Hip fracture remains a major problem for older persons, resulting in not only a decline in function but also in an increase in mortality (56–60). Whereas calcium and vitamin D have been shown to decrease hip fracture in nursing home residents and the once-a-week alendronate has markedly decreased hip fractures (61), we can hope to see drugs that will more dramatically increase bone mass and strengthen its architecture. One such group of drugs may well be parahormone analogs (62).

Elevated cytokines have been implicated in declining function in older persons (18,63,64). Cytokines are also thought to play a role in cachexia (37,38,65). Cytokine antagonists are in clinical use to treat rheumatoid arthritis (66). They clearly have potential to be used for muscle wasting and the anorexia of older persons (vide infra).

The anorexia of aging, and the associated weight loss and malnutrition, represent a major problem for many older individuals (67–69). Whereas early recognition, treatment of the causes, and the potential use of appetite enhancers (70) all represent useful approaches, there is clearly a need for the development of orexigenic drugs (71). Megestrol acetate increases food intake, most probably by inhibiting cytokines (72). Its side effects include suppression of testosterone and cortisol. Dronabinol is the active ingredient of cannabis. It enhances appetite, suppresses nausea, and improves mood in some persons (73). Clearly, there is a need for the development of other drugs in this area. One possibility is the development of a cholecystokinin antagonist to inhibit the elevated levels that are seen in older persons (74). Leptin is an anorectic peptide (75) whose levels increase in older men (76). Leptin antagonists, therefore, are a potential group of orexigenic drugs.

Postprandial hypotension is a common condition in older persons (77–79). It is associated with falls, syncope, and myocardial infarction (80). Calcitonin gene-related peptide is a peptide hormone whose increase has been associated with postprandial hypotension (81). Development of antagonists to this peptide represent a potential area for the management of postprandial hypotension.

Other areas where drug development is moving forward (and we should, hopefully, soon have drugs that are useful to our patients) are the use of growth factors in the treatment of pressure ulcers (82), the management of sleep disturbances in older persons (83,84), the treatment of depression (85,86), and the development of new drugs specifically targeted at the genetic abnormalities in some cancers (87,88).

An area where drug treatments may have a particularly dramatic effect on functional status is diabetes mellitus. A number of recent studies have found that diabetics are particularly vulnerable to develop functional impairment and injurious falls (89–91). Diabetes is a major predictor of lower body function, which in turn predicts mortality (92,93). In the last 5 years, numerous new drugs for the treatment of diabetes have been marketed, and aggressive management of diabetes and its associated hypertension has been demonstrated to decrease mortality (94). In addition, the recent discovery of resistin, a hormone that inhibits insulin effects, has opened up another Pandora's box for drugs that may be useful in treating diabetes (95).

Urinary incontinence is an extremely common condition in older persons, and it can impinge dramatically on their quality of life (96–100). Management of urinary incontinence, despite dramatic advances in the last decade, remains unsatisfactory for many patients. The need to find adequate drug therapies with minimal side effects for urge and stress incontinence as well as lower urinary tract symptomatology is a key area in geriatric pharmacology.

Dietary restriction has long been one of the approaches shown to prolong lifespan (101–103). Recent studies in baboons have suggested that caloric restriction may merely be reducing excessively overweight animals to a level of body fat closer to that seen in the wild (104). This suggests that utilizing drugs that mimic caloric restriction may prolong life (105–107). These would include drugs that decrease weight, decrease oxidative stress, increase insulin sensitivity, and modulate the neuroendocrine system in ways similar to caloric restriction. In addition, the understanding of the genetic variability in responses to caloric restriction will be key in tailoring the drug to the individual (108). Clearly, this is an area of great potential for future drug development.

Finally, it should be remembered that the majority of older patients use herbal and/or vitamin supplements (109–113). These can interact with prescription drugs and have a whole series of side effects of their own. In addition, some of these herbals, such as valerian for sleep and gingko biloba for memory problems, appear to be efficacious. Thus, we can expect to see the appearance of drugs based on the active ingredients in some of these herbal medications.

Although it is clear that the future of drug development to enhance the function of older persons is extremely exciting, those of us who care for older persons need to remember that most drugs come with a set of side effects, many of which the older population are particularly vulnerable to developing. Although drugs should be used judiciously in the older population, it is important to remember that "high touch" often is more important then "high tech" approaches in the older person. Our *Journal* will do its best to provide you a balanced approach to the rapidly developing field of drug development for older persons over the next few years.

Because this is the first editorial of the year, I will use it also to update you on the *Journal*, as I have in previous years (114). We are happy to announce that there was a marked increase in the Citation Index of the *Journal* in 2000, from 1.222 to 1.569. This increase moved the *Journal* from 12th to 9th among the geriatric journals. The *Journal* continues to give rapid reviews with the mean time to first decision being 9 days and a range of 1 to 68 days. Our rejection rate, unfortunately, remains high at 62%. This in no way reflects the quality of the articles we receive, but rather a lack of space to publish many of the excellent submissions we receive at the *Journal*. Finally, I would like to encourage our readership to send letters commenting on their views of drugs for the elderly population or on other articles in the *Journal*. Only if you do this can the *Journal* truly be your voice.

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References

1. Beers MH. The medication list—a portrait of a patient's health. *J Gerontol Med Sci.* 2000;55A:M549.
2. Edelberg HK, Shallenberger E, Hausdorff JM, Wei JY. One-year follow-up of medication management capacity in highly functioning older adults. *J Gerontol Med Sci.* 2000;55A:M550–M553.
3. Flaherty JH, Perry HM, Lynchard GS, Morley JE. Polypharmacy and hospitalization among older home care patients. *J Gerontol Med Sci.* 2000;55A: M554–M559.
4. Flaherty JH. Who's taking your 5th vital sign? *J Gerontol Med Sci*. 2001;56A:M397–M399.
5. Singh NA, Clements KM, Singh MAF. The efficacy of exercise as a long-term antidepressant in elderly subjects: a randomized, controlled trial. *J Gerontol Med Sci.* 2001;56A:M497–M504.
6. Baldwin AC, Stevenson SW, Dudley GA. Nonsteroidal anti-inflammatory therapy after eccentric exercise in healthy older individuals. *J Gerontol Med Sci.* 2001;56A:M510–M513.
7. Ince A. The use of COX-2 specific inhibitors: is it all hype or is it evidence based? *J Gerontol Med Sci*. 2001;56A:M136–M137.
8. Lisse J, Espinoza L, Zhao SZ, Dedhiya SD, Osterhaus JT. Functional status and health-related quality of life of elderly osteoarthritic patients treated with celecoxib. *J Gerontol Med Sci.* 2001;56A:M167–M175.
9. Wilcox CM, Heudebert G, Klapow J, Shewchuk R, Casebeer L. Survey of primary care physicians' approach to gastroesophageal reflux disease in elderly patients. *J Gerontol Med Sci.* 2001;56A:M514–M517.
10. Dellasega C, Orwig D, Ahern F, Lenz E. Postdischarge medication use of elderly cardiac patients from urban and rural locations. *J Gerontol Med Sci.* 1999;54A:M514–M520.
11. Newman SC, Hassan AI. Antidepressant use in the elderly population in Canada: results from a national survey. *J Gerontol Med Sci.* 1999;54A: M527–M530.
12. Incalzi RA, Pedone C, Pahor M, Carosella L, Bernabei R, Carbonin P. Reasons of prompting digitalis therapy in the acute care hospital. *J Gerontol Med Sci.* 2001;56A:M361–M365.
13. Rigaud AS, Forette B. Hypertension in older adults. *J Gerontol Med Sci.* 2001;56A:M217–M225.
14. Rich MW. Heart failure in the 21st century: a cardiogeriatric syndrome. *J Gerontol Med Sci.* 2001;56A:M88–M96.
15. Meneilly GS, Tessier D. Diabetes in elderly adults. *J Gerontol Med Sci.* 2001;56A:M5–M13.
16. Morley JE. Diabetes mellitus: a major disease of older persons. *J Gerontol Med Sci*. 2000;55A:M255–M256.
17. Chin MH, Su AW, Jin L, Nerney MP. Variations in the care of elderly persons with diabetes among endocrinologists, general internists, and geriatricians. *J Gerontol Med Sci.* 2000;55A:M601–M606.
18. Aronow WS. Treatment of older persons with hypercholesterolemia with and without cardiovascular disease. *J Gerontol Med Sci.* 2001;56A:M138–M145.
19. Castano G, Mas R, Fernandez JC, Illnait J, Fernandez L, Alvarez E. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J Gerontol Med Sci.* 2001;56A:M186–M192.
20. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Med Sci.* 2001;56A:M146–M156.
21. Gillick M. Pinning down frailty. *J Gerontol Med Sci*. 2001;56A:M134–M135.
22. Cohen HJ. In search of the underlying mechanisms of frailty. *J Gerontol Med Sci.* 2000;55A:M706–M708.
23. Evans WJ. Exercise strategies should be designed to increase muscle power. *J Gerontol Med Sci*. 2000;55A:M309–M310.
24. Keysor JJ, Jette AM. Have we oversold the benefit of late-life exercise? *J Gerontol Med Sci.* 2001;56A:M412–M423.
25. Westerterp KR, Meijer EP. Physical activity and parameters of aging: a physiological perspective. *J Gerontol Biol SciMed Sci*. 2001;56A(Special Issue II):M7–M12.
26. Rubenstein LZ, Josephson KR, Trueblood PR, et al. Effects of a group exercise program on strength, mobility, and falls among fall-prone elderly men. *J Gerontol Med Sci.* 2000;55A:M317–M321.
27. Hagerman FC, Walsh SJ, Staron RS, et al. Effects of high-intensity resistance training on untrained older men. I. Strength, cardiovascular, and metabolic responses. *J Gerontol Biol Sci.* 2000;55A:B336–B346.
28. Ivey FM, Tracy BL, Lemmer JT, et al. Effects of strength training and detraining on muscle quality: age and gender comparisons. *J Gerontol Biol Sci.* 2000;55:B152–B157.
29. Gardner AW, Katzel LI, Sorkin JD, et al. Improved functional outcomes following exercise rehabilitation in patients with intermittent claudication. *J Gerontol Med Sci.* 2000;55A:M570–M577.
30. Rejeski WJ, Mihalko SL. Physical exercise and quality of life in older adults. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue II):M23–M35.
31. Hughes VA, Frontera WR, Wood M, et al. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. *J Gerontol Biol Sci.* 2001;56A:B209–B217.
32. Bard F, Cannon C, Barbour R, et al. Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med.* 2000;6:916–919.
33. Morley JE, Kumar VB, Bernardo AE, et al. Beta-amyloid precursor polypeptide in SAMP8 mice affects learning and memory. *Peptides.* 2000;21:1761–1767.
34. Kumar VB, Farr SA, Flood JF, et al. Site-directed antisense oligonucleotide decreases the expression of amyloid precursor protein and reverses deficits in learning and memory in aged SAMP8 mice. *Peptides.* 2000;21:1769–1775.

35. Kumar VB, Vyas K, Franko M, et al. Molecular cloning, expression, and regulation of hippocampal amyloid precursor protein of senescence accelerated mouse (SAMP8). *Biochem Cell Biol.* 2001;79:57–67.
36. Banks WA, Farr SA, Butt W, Kumar VB, Franko MW, Morley JE. Delivery across the blood-brain barrier of antisense directed against amyloid beta: reversal of learning and memory deficits in mice overexpressing amyloid precursor protein. *J Pharmacol Exp Ther.* 2001;297:1113–1121.
37. Royall DR, Chiodo LK, Polk MJ. Correlates of disability among elderly retirees with "subclinical" cognitive impairment. *J Gerontol Med Sci.* 2000; 55A:M541–M546.
38. Roubenoff R, Hughes VA, Dallal GE, et al. The effect of gender and body composition method on the apparent decline in lean mass-adjusted resting metabolic rate with age. *J Gerontol Med Sci.* 2000;55A:M757–M760.
39. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. *J Lab Clin Med.* 2001;137:231–243.
40. Morley JE. Anorexia, sarcopenia, and aging. *Nutrition*. 2001;17:660–663.
41. Schlicht J, Camaione DN, Owen SV. Effect of intense strength training on standing balance, walking speed, and sit-to-stand performance in older adults. *J Gerontol Med Sci*. 2001;56A:M281–M286.
42. Foldvari M, Clark M, Laviolette LC, et al. Association of muscle power with functional status in community-dwelling elderly women. *J Gerontol Med Sci.* 2000;55A:M192–M199.
43. Bartke A, Coschigano K, Kopchick J, et al. Genes that prolong life: relationships of growth hormone and growth to aging and life span. *J Gerontol Biol Sci.* 2001;56A:B340–B349.
44. Morley JE. Growth hormone: fountain of youth or death hormone? *J Am Geriatr Soc.* 1999;47:1475–1476.
45. Morley JE, Kaiser FE, Perry HM, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism*. 1997;46:410–413.
46. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev.* 1999;107:123–136.
47. Sih R, Morley JE, Kaiser FE, Perry HM, Patrick P, Ross C. Testosterone replacement in older hypogonadal men—a 12-month randomized controlled trial. *J Clin Endocrinol Metab.* 1997;82:1661–1667.
48. Urban RJ, Bodenburg YH, Gilkison C, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol.* 1995;32:E820–E826.
49. Morley JE, Perry HM III, Kaiser FE, et al. Effects of testosterone replacement therapy in older hypogonadal males: a preliminary study. *J Am Geriatr Soc.* 1993;41:149–152.
50. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol Med Sci.* 2001;56A:M266–M272.
51. Morley JE. Andropause: is it time for the geriatrician to treat it? *J Gerontol Med Sci.* 2001;56A:M263–M265.
52. Kamel HK, Perry HM, Morley JE. Hormone replacement therapy and fractures in older adults. *J Am Geriatr Soc.* 2001;49:179–187.
53. Katz MS. Geriatrics grand rounds: Eve's rib, or a revisionist view of osteoporosis in men. *J Gerontol Med Sci.* 2000;55A:M560–M569.
54. Kenny AM, Prestwood KM, Marcello KM, Raisz LG. Determinants of bone density in healthy older men with low testosterone levels. *J Gerontol Med Sci.* 2000;55A:M492–M497.
55. Christmas C, O'Connor KG, Harman SM, et al. Growth hormone and sex steroid effects on bone metabolism and bone mineral density in healthy aged women and men. *J Gerontol Med Sci*. In press.
56. Michel JP, Hoffmeyer P, Klopfenstein C, Bruchez M, Grab B, d'Epinay CL. Prognosis of functional recovery 1 year after hip fracture: typical patient profiles through cluster analysis. *J Gerontol Med Sci.* 2000;55A:M508–M515.
57. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. *J Gerontol Med Sci.* 2000;55A:M498–M507.
58. Perry HM. Facets of femoral fracture. *J Gerontol Med Sci*. 2000;55A:M487–M488.
59. Overend TJ, Chesworth BM, Sandrin M, Stroud S, Petrella RJ, McCalden R. Determination of prefracture physical function in community-dwelling people who fracture their hip. *J Gerontol Med Sci.* 2000;55A:M698–M702.
60. Frassetto LA, Todd KM, Morris RC, Sebastian A. Worldwide incidence of hip fracture in elderly women: relation to consumption of animal and vegetable food. *J Gerontol Med Sci.* 2000;55A:M585–M592.
61. Banks WA, Morley JE. Endocrine and metabolic changes in human aging. *J Am Aging Assoc.* 2000;23:103–115.
62. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434–1441.
63. Beharka AA, Meydani M, Wu DY, Leka LS, Meydani A, Meydani SN. Interleukin-6 production does not increase with age. *J Gerontol Biol Sci.* 2001; 56A:B81–B88.
64. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur Studies of Successful Aging. *J Gerontol Med Sci.* 2000;55A:M709–M715.
65. Morley JE. Decreased food intake with aging. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue II):M81–M88.
66. Richard-Miceli C, Dougados M. Tumour necrosis factor-alpha blockers in rheumatoid arthritis—review of the clinical experience. *BioDrugs*. 2001; 15:251–259.
67. Wilson MMG. Bitter-sweet memories: truth and fiction. *J Gerontol Med Sci*. 2001;56A:M196–M199.
68. MacIntosh C, Morley JE, Chapman IM. The anorexia of aging. *Nutrition.* 2000;16:983–995.
69. Amarantas E, Martinez A, Dwyer J. Nutrition and quality of life in older adults. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue II):M54–M64.
70. Thomas DR, Ashmen W, Morley JE, Evans WJ. Nutritional management in long-term care: development of a clinical guideline. *J Gerontol Med Sci.* 2000;55A:M725–M734.
71. Morley JE. Anorexia of aging—physiologic and pathologic. *Am J Clin Nutr.* 1997;66:760–773.
72. Yeh SS, Wu SY, Levine DM, et al. The correlation of cytokine levels with body weight after megestrol acetate treatment in geriatric patients. *J Gerontol Med Sci.* 2001;56A:M48–M54.
73. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of Dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry.* 1997;12:913–919.
74. MacIntosh CG, Andrews JM, Jones KL, et al. Effects of age on concentrations of plasma cholecystokinin, glucagons-like peptide 1, and peptide YY and their relation to appetite and pyloric motility. *Am J Clin Nutr.* 1999;69:999–1006.
75. Morley JE, Perry HM, Baumgartner RP, Garry PJ. Leptin, adipose tissue and aging: is there a role for testosterone? *J Gerontol Biol Sci.* 1999;54A:B108–B109.
76. Baumgartner RN, Ross RR, Waters DL, et al. Serum leptin in elderly people: associations with sex hormones, insulin, and adipose tissue volumes. *Obes Res.* 1999;7:141–149.
77. Puisieux F, Bulckaen H, Fauchais AL, Drumez S, Salomez-Granier F, Dewailly P. Ambulatory blood pressure monitoring and postprandial hypotension in elderly persons with falls or syncopes. *J Gerontol Med Sci*. 2000;55A:M535–M540.
78. Mehagnoul-Schipper DJ, Boerman RH, Hoefnagels WHL, Jansen RWMM. Effect of levodopa on orthostatic and postprandial hypotension in elderly parkinsonian patients. *J Gerontol Med Sci*. 2001;56A:M749–M755.

79. Vloet LCM, Mehagnoul-Schipper DJ, Hoefnagels WHL, Jansen RWMM. The influence of low-, normal- and high carbohydrate meals on blood pressure in elderly patients with postprandial hypotension. *J Gerontol Med Sci*. 2001;56A:M744–M748.
80. Morley JE. Postprandial hypotension: the ultimate Big Mac attack. *J Gerontol Med Sci*. 2001;56A:M741–M743.
81. Edwards BJ, Perry HM, Kaiser FE, et al. Relationship of age and calcitonin gene-related peptide to postprandial hypotension. *Mech Ageing Dev*. 1996; 87:61–73.
82. Thomas DR, Ashmen W, Morley JE, Evans WJ. Nutritional management in long-term care: development of a clinical guideline. *J Gerontol Med Sci.* 2000;55A:M725–M734.
83. Babar SI, Enright PL, Boyle P, et al. Sleep disturbances and their correlates in elderly Japanese American men residing in Hawaii. *J Gerontol Med Sci.* 2000;55A:M406–M411.
84. Middlekoop HAM, Smildevandendoel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50–93: effects of sex and age, and factors related to self-evaluated quality of sleep. *J Gerontol Med Sci.* 1996;51A:M108–M115.
85. Draganich LF, Zacny J, Klafta J, Karrison T. The effects of antidepressants on obstructed and unobstructed gait in healthy elderly people. *J Gerontol Med Sci.* 2001;56A:M36–M41.
86. Blazer DG, Hybels CF, Pieper CF. The association of depression and mortality in elderly persons: a case for multiple, independent pathways. *J Gerontol Med Sci.* 2001;56A:M505–M509.
87. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031–1037.
88. Goldman JM, Melo JV. Targeting the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344(14):1084–1086.
89. Miller DK, Carter ME, Sigmund RH, et al. Nutritional risk in inner-city-dwelling older black Americans. *J Am Geriatr Soc.* 1996;44:959–962.
90. Nourhashemi F, Andrieu S, Gillette-Guyonnet S, Vellas B, Albarede JL, Grandjean H. Instrumental activities of daily living as a potential marker of frailty: a study of 7364 community-dwelling elderly women (The EPIDOS Study). *J Gerontol Med Sci.* 2001;56:M448–M453.
91. Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. *J Gerontol Med Sci.* 2000;55A:M84–M89.
92. Resnick HE, Vinik AI, Heimovitz HK, Brancati FL, Guralnik JM. Age 85+ years accelerates large-fiber peripheral nerve dysfunction and diabetes contributes even in the oldest-old: the Women's Health and Aging Study. *J Gerontol Med Sci.* 2001;56A:M2–M31.
93. Caruso LB, Silliman RA, Demissie S, Greenfield S, Wagner EH. What can we do to improve physical function in older persons with type 2 diabetes? *J Gerontol Med Sci.* 2000;55A:M372–M377.
94. Morley JE. An overview of diabetes mellitus in older persons. *Clin Geriatr Med.* 1999;15:211.
95. Steppan CM, Bailey ST, Ghat S, et al. The hormone resistin links obesity to diabetes. *Nature*. 2001;409:307–312.
96. Diokno AC. Epidemiology of urinary incontinence. *J Gerontol Med Sci*. 2001;56A:M3–M4.
97. Maggi S, Minicuci N, Langlois J, Pavan M, Enzi G, Crepaldi G. Prevalence rate of urinary incontinence of community-dwelling elderly individuals: the Veneto study. *J Gerontol Med Sci*. 2001;56A:M14–M18.
98. Miles TP, Palmer RF, Espino DV, Mouton CP, Lichtenstein MJ, Markides KS. New-onset incontinence and markers of frailty: data from the Hispanic established populations for epidemiologic studies of the elderly. *J Gerontol Med Sci.* 2001;56A:M19–M24.
99. Iglesias FJG, Ocerin JMCY, Martin JPDM, et al. Prevalence and psychosocial impact of incontinence in older people of a Spanish rural population. *J Gerontol Med Sci.* 2000;55A:M207–M214.
100. Fultz NH, Herzog AR, Raghunathan TE, Wallace RB, Diokno AC. Prevalence and severity of urinary incontinence in older African American and Caucasian women. *J Gerontol Med Sci.* 1999;54A:M299–M303.
101. Hadley EC, Dutta C, Finkelstein J, et al. Human implications of caloric restrictions' effects on aging in laboratory animals: an overview of opportunities for research. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue):5–6.
102. Lee IM, Blair SN, Allison DB, et al. Epidemiologic data on the relationships of caloric intake, energy balance, and weight gain over the life span with longevity and morbidity. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue I):7–19.
103. Roberts SB, Pi-Sunyer X, Kuller L, et al. Physiologic effects of lowering caloric intake in nonhuman primates and nonobese humans. *J Gerontol Biol Sci Med Sci*. 2001;56(Special Issue II):66–75.
104. Banks WA, Phillips-Conroy JE, Jolly CJ, Morley JE. Serum leptin levels in wild and captive populations of baboons (Papio): implications for the ancestral role of leptin. *J Endocrin Metab.* In press.
105. Weindruch R, Keenan KP, Carney JM, et al. Caloric restriction mimetics: metabolic interventions. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue I):20–33.
106. Mobbs CV, Bray GA, Atkinson RL, et al. Neuroendocrine and pharmacological manipulations to assess how caloric restriction increases life span. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue I):34–44.
107. Poehlman ET, Turturro A, Bodkin N, et al. Caloric restriction mimetics: physical activity and body composition changes. *J Gerontol Biol Sci Med Sci*. 2001;56A(Special Issue I):45–54.
108. Allison DB, Miller RA, Austad SN, et al. Genetic variability in responses to caloric restriction in animals and in regulation of metabolism and obesity in humans. *J Gerontol Biol Sci Med Sci*. 2001;56(Special Issue I):55–65.
109. Astin JA, Pelletier KR, Marie A, Haskell WL. Complementary and alternative medicine use among elderly persons: one-year analysis of a Blue Shield Medicare supplement. *J Gerontol Med Sci.* 2000;55A:M4–M9.
110. Vitolins MZ, Quandt SA, Case LD, Bell RA, Arcury TA, McDonald J. Vitamin and mineral supplement use by older rural adults. *J Gerontol Med Sci.* 2000;55A:M613–M617.
111. Flaherty JH, Takahashi R, Teoh J, et al. Use of alternative therapies in older outpatients in the United States and Japan: prevalence, reporting patterns, and perceived effectiveness. *J Gerontol Med Sci*. 2001;56A:M650–M655.
112. Loera JA, Black SA, Markides KS, Espino DV, Goodwin JS. The use of herbal medicine by older Mexican Americans. *J Gerontol Med Sci*. 2001; 56A:M714–M718.
113. Wakimoto P, Block G. Dietary intake, dietary patterns, and changes with age: epidemiological perspective. *J Gerontol Bio Sci Med Sci*. 2001;56(Special Issue II):M65–M80.
114. Morley JE. The state of the Journal. *J Gerontol Med Sci.* 2001;56A:M2.