Organ Reserve and Healthy Aging

John Neustadt, ND, and Steve Pieczenik, MD, PhD

Aging is a complex physical, social, economic, and psychological process with major medical, legal, economic, and public health policy challenges. The US Department of Health and Human Services Administration on Aging estimates that more than 1 in every 8 Americans is now over age 65. As of 2006, this age group represented 12.4% of the population, but by 2030 this number will increase to 20%.[1] As the US population comes closer to this mark, issues related to aging are becoming more and more prevalent in public political debates and healthcare policy discussions—a positive note since the issues require immediate attention if we are to adequately care for our ever-growing elderly population.

Two important medical concerns for clinicians to consider are how to help people age healthfully to maximize vitality into old age and how to determine possibilities for restoring vitality in the elderly. One way to approach this question is to examine organ-specific declines in function and address how to improve their functions.

Organs are thought to have a certain capacity to withstand perturbations and return to homeostasis, a concept that has been termed "organ reserve." This reserve declines with age and may explain some functional deterioration in the elderly, such as decreases in strength, balance, and cognition. In fact, it has been estimated that reserve capacity in a healthy young adult is 7 to 11 times greater than the average demand, but, by age 85, organ reserve has been reduced to 50% of its original capacity.[2]

Originally, this notion was based primarily on observational data that attempted to explain the underlying mechanisms behind what is called Gompertz's Law. This theory was postulated in 1825 by Benjamin Gompertz, a British actuary who analyzed mortality data and concluded that the rate of mortality doubles every 7 years beyond age 30.[3] In 1960, Bernard Strehler and Albert Mildvan, 2 researchers who at that time were on the staff of the National Institutes of Health's Gerontology Branch, created their General Theory of Mortality and Aging, a rather impressive mathematical formula that attempts to quantify the relationship between age and death rate.[4] Their work centered on explaining the observation that, beyond age 30, physiological function declines at a rather consistent and linear rate of 0.5% to 1.3% annually.[4]

A central postulate in the General Theory of Mortality and Aging is, "An organism contains a number of subsystems, each of which has a certain maximum ability to restore initial conditions after a challenge (that is, a change in condition due to internal or external energy fluctuations). Death occurs when the rate at which an organism does work to restore the original state is less than that demanded to overcome the effects of a given challenge." These combined observations by Gompertz, Strehler, and Mildvan are frequently cited in published geriatrics research, and the concept of organ reserve is found in both popular[5-7] and medical[8-10] books.

Physicians observe in patients that physiological stressful situations (eg, disease, surgery, medications) strain reserve capacity and hinder the ability to compensate for increased metabolic demand, resulting in compromised function.[11] However, studies demonstrating this phenomenon are lacking. More commonly, observational data demonstrating changes in organ mass or function are cited as evidence for organ reserve.

Clinical Evidence

While a large body of observational data exists to support the concept of organ reserve, there is very little evidence from clinical trials that verifies this notion. One clinical trial that attempted to evaluate the question of organ reserve was conducted in 2003 by EM Ghezzi and JA Ship, from University of Michigan School of Dentistry and New York University College of Dentistry, respectively. This team studied changes in the reserve capacity of salivary glands with age.[12] In a randomized, double-blind, placebo-controlled, crossover design, they compared the ability of salivary glands to recover after administration of 4.0 µg/kg intravenous glycopyrrolate, a muscarinic receptor antagonist that inhibits salivation, in 18 young (20-38 years old) and 18 elderly (60-77 years old) healthy adults. The researchers measured salivary flow rates from the parotid and submandibular-sublingual glands. The mean time for parotid gland salivary flow rates to return to baseline in the young age group was 189.4 ± 119.3 minutes and in the elderly group was 318.5 ± 75.7 minutes. This difference was highly statistically significant (P=.002).

For the submandibular-sublingual glands, the mean time to recovery was 187.5 ± 103.8 minutes vs 275.8 ± 93.9 minutes for the young and elderly groups, respectively (P=.01). The total duration of suppression was also significantly greater in the elderly group compared with the young subjects. The mean total duration of suppression for the parotid gland was 156.7 ± 127.6 minutes vs 289.7 ± 102.6 minutes for the young and elderly groups, respectively (P=.002), and 164.2 ± 105.0 minutes versus 263.6 ± 98.1 for the submandibular-sublingual glands in young compared with elderly subjects, respectively (P=.01).

According to Ghezzi and Ship, "many older adults complain of dry mouth and experience deleterious consequences of this condition, which can include sore throat, dysphonia, dysphagia, periodontal disease, oral candidiasis, dysgeusia, glossodynia, increased need to drink water, cheilitis, inflammation or ulcers of the tongue and buccal mucosa, halitosis, and salivary gland infections."[12] While prospective and longitudinal studies of healthy adults have shown that salivary gland function is age-stable in this population,[13,14] medications, systemic disease,

chemotherapy, and head and neck radiation treatment can all decrease saliva production.[15]

Although not discussed by Ghezzi and Ship in their study, the possibility that decreased saliva production may be caused by decreased drug clearance—a well-known cause for age-related, medication-induced toxicities—cannot be ruled out.[16] This may, in fact, explain the increased recovery time for salivary glands in the elderly volunteers given glycopyrrolate in the study.

Despite the fact that many articles in peer-reviewed medical journals discuss organ reserve,[17-20] what they actually describe is not a decrease in the ability of an organ to recover from trauma; rather, they are referring simply to a general decline in organ mass or function. Technically, however, a simple decrease in organ mass or function does not prove the decline of organ reserve, which, strictly defined, is "to restore homeostasis [after a perturbation] and maintain it within narrow confines necessary for preservation of life."[2] Admittedly, this is a very difficult concept to test and does not lend itself readily to the double-blind, placebo-controlled clinical trial—the gold standard of today's research paradigm. While there is a paucity of data supporting the concept of organ reserve, a lack of clinical trials does not disprove the concept. Organ reserve may, in fact, be a verifiable phenomenon and may explain why the elderly are more susceptible to death from surgery, sepsis, falls, medication side effects, and disease.

In any given person, different organs, tissues, and cell types are affected by aging in unique ways controlled by complex interactions among genetics, nutritional status, medications, and stressors (environmental, physical, and emotional). Decreases in organ mass, tissue anatomy, and physiological function with age have been demonstrated in the human heart,[20] brain,[21] liver,[22] kidney,[23] salivary glands,[12] stomach,[24] and muscle tissue.[25]

For example, research shows that people with chronic cortisol elevations have a nearly 20% destruction of their hippocampus as well as destruction of the frontal lobe.[26] As another example, the greatest storage reservoir of protein in the body is muscle; however, with age, muscle mass and strength tend to be lost. By age 70, voluntary muscle contractile strength decreases by 20% to 40% in both men and women.[27] Starting in the fourth decade of life, knee extension strength tends to decline by 8% to 10% per decade in both men and women.[28] By the time men and women are in their 7th or 8th decade of life, on average they have lost 20% to 40% of the contractile strength of voluntary muscles, and 50% by the 9th decade.[27]

The brain shows a decrease of viable cells with age, amounting in some areas to a 25% to 30% decrease, and a decrease in brain tissue of 9% to 17%.[21] This may, indeed, explain functional decline in mental status, and may, in fact, result in a decreased ability to recover from a perturbation (organ reserve), but data appear nonexistent to confirm or refute this idea.

Similarly, renal mass tends to decrease with advancing age. From birth to young adulthood, renal mass increases from about 50 g to 400 g, then decreases to 300 g in the 9th decade.[23] However, multiple studies evaluating the health of elderly volunteers enrolled as kidney donors showed that glomerular filtration rate did not decline with age.[23]

Even if organ reserve is a real phenomenon, the level of maximal organ reserve does not necessarily correlate with chronological age because both the onset and the progression of decline show profound individual variations.[4] A 1955 study by Martin Brandfonbrener, Milton Landowne, and Nathan W. Shock published in the journal *Circulation* demonstrated this concept.[29] They measured cardiac output in 67 male volunteers aged 19 to 86 years (average 52.5 years) with no diagnosed circulatory disorders. In regression analysis, cardiac output showed a significant average decline of approximately 1% per year after the third decade of life ($P<.001$), but the standard deviation was 21.8%. This large standard deviation means that many participants had much lower or higher rates of decline.

Conclusion

Since Gompertz first plotted mortality with age, the concept of declining organ reserve has come to be commonly accepted as the underlying cause of this trend. While this may be the case, it has never been demonstrated definitively. Research does support the notion of decreased organ mass and function with age, but the rate and severity of decline varies between individuals and even between specific organs within individuals and does not always correlate with age. In fact, clinical trials have shown that declines in organ mass and function are reversible in some tissues, such as muscle and brain.[30, 31] This fact points to the crucial role nutrition plays in aging, which should be a major focus of geriatric research. In a future article we will review how specific nutrients, botanicals, hormone replacement therapy, or dietary and lifestyle interventions may slow or even reverse the aging process. In some ways, whether or not organ reserve is real is more a philosophical question. No matter what the reason, given the rapid increase of our elderly population, our national research agenda and clinical mandate should be the aggressive pursuit of ways to improve functional capacity in the elderly.

John Neustadt, ND, is clinic director of Montana Integrative Medicine and president and CEO of Nutritional Biochemistry, Incorporated (NBI), and NBI Testing and Consulting Corp (NBITC), in Bozeman, Mont. Dr Neustadt has published more than 100 research reviews, is coauthor with Steve Pieczenik, MD, PhD, of the book *A Revolution in Health through Nutritional Biochemistry*, and is editor of the next edition of the textbook *Laboratory Evaluations for Integrative and Functional Medicine*.

Steve Pieczenik, MD, PhD, trained in psychiatry at Harvard and has an MD from Cornell University Medical College and a PhD in International Relations from Massachusetts Institute of Technology. He is a board-certified psychiatrist and was a board examiner in psychiatry and neurology. He is chairman of the board of NBI and NBITC.

References

1. US Department of Health and Human Services. Administration on Aging. *A Profile of Older Americans: 2006.* Washington, DC: US Dept of Health and Human Services; 2006.
2. Manhapra A. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes: an alternate take from a generalist. *J Am Coll Cardiol.* 2004;43(5):924.
3. Hayflick L. Cell biology of aging. *BioScience.* 1975;25(10):629-637.
4. Strehler BL, Mildvan AS. General theory of mortality and aging. *Science.* Jul 1 1960;132:14-21.
5. Bland J. *Genetic Nutritioneering*. Lincolnwood, IL: Keats; 1999.
6. Hyman M, Liponis M. *Ultraprevention: The 6-Week Plan That Will Make You Healthy for Life*. New York, NY: Atria; 2005.

7. Giampapa VC, Williamson ME. *Breaking the Aging Code: Maximizing Your DNA Function for Optimal Health and Longevity*. North Bergen, NJ: Basic Health Publications; 2003.
8. Karasek M, ed. *Aging and Age-Related Diseases: The Basics*. Hauppauge, NY: Nova Science Publishers; 2006.
9. Maddox GL, Atchley RC, Evans JG, eds. *The Encyclopedia of Aging: A Comprehensive Resource in Gerontology and Geriatrics.* 3rd ed. New York, NY: Springer Publishing Company, Inc; 2001.
10. Rosenthal RA, Zenilman ME, Katlic MR, eds. *Principles and Practice of Geriatric Surgery*. New York, NY: Springer-Verlag; 2001.
11. Evers BM, Townsend CM Jr, Thompson JC. Organ physiology of aging. *Surg Clin North Am.* 1994;74(1):23-39.
12. Ghezzi EM, Ship JA. Aging and secretory reserve capacity of major salivary glands. *J Dent Res.* 2003;82(10):844-848.
13. Ghezzi EM, Wagner-Lange LA, Schork MA, et al. Longitudinal influence of age, menopause, hormone replacement therapy, and other medications on parotid flow rates in healthy women. *J Gerontol A Biol Sci Med Sci.* 2000;55(1):M34-M42.
14. Ship JA, Nolan NE, Puckett SA. Longitudinal analysis of parotid and submandibular salivary flow rates in healthy, different-aged adults. *J Gerontol A Biol Sci Med Sci.* 1995;50(5):M285-M289.
15. Ship JA, Pillemer SR, Baum BJ. Xerostomia and the geriatric patient. *J Am Geriatr Soc.* 2002;50(3):535-543.
16. Mühlberg W, Platt D. Age-dependent changes of the kidneys: pharmacological implications. *Gerontology.* 1999;45(5):243-253.
17. Fries JF, Singh G, Morfeld D, Hubert HB, Lane NE, Brown BW Jr. Running and the development of disability with age. *Ann Intern Med.* 1994;121(7):502-509.
18. Epstein M. Aging and the kidney. *J Am Soc Nephrol.* 1996;7(8):1106-1122.
19. Fries JF. Aging, cumulative disability, and the compression of morbidity. *Compr Ther.* 2001;27(4):322-329.
20. Montgomery H. Cardiac reserve: linking physiology and genetics. *Intensive Care Med.* 2000;26 Suppl 1:S137-S144.
21. Sinex FM. Biochemistry of aging. *Science.* Nov 3 1961;134:1402-1405.
22. Schmucker DL. Aging and the liver: an update. *J Gerontol A Biol Sci Med Sci.* 1998;53(5):B315-B320.
23. Epstein M. Aging and the kidney. *J Am Soc Nephrol.* 1996;7(8):1106-1122.
24. Saltzman JR, Russell RM. The aging gut. Nutritional issues. *Gastroenterol Clin North Am.* 1998;27(2):309-324.
25. Nair KS. Aging muscle. *Am J Clin Nutr.* 2005;81(5):953-963.
26. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry.* 2000;157(1):115-118.
27. Doherty TJ. Invited review: Aging and sarcopenia. *J Appl Physiol.* 2003;95(4):1717-1727.
28. Lindle RS, Metter EJ, Lynch NA, et al. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. *J Appl Physiol.* 1997;83(5):1581-1587.
29. Brandfonbrener M, Landowne M, Shock NW. Changes in cardiac output with age. *Circulation.* 1955;12(4):557-566.
30. Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. *Am J Clin Nutr.* 2003;78(2):250-258.
31. Malaguarnera M, Cammalleri L, Gargante MP, Vacante M, Colonna V, Motta M. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr.* 2007;86(6):1738-1744.