

8. Christou NV, Sampalis JS, Liberman M, et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg* 2004;240:416-23.
9. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
10. Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003;24:610-28.
11. Sjöström L, Lindroos A-K, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683-93.
12. Pories WJ, MacDonald KG, Flickinger EG, et al. Is type II diabetes mellitus (NIDDM) a surgical disease? *Ann Surg* 1992;215:633-42.
13. O'Brien PE, Dixon JB, Laurie C, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med* 2006;144:625-33.

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Sex and Aging

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Human beings are living longer, women more so than men. Among people 85 years of age and older, there are 4 men for every 10 women.¹ What happens to sexuality in older age?

In this issue of the *Journal*, Lindau et al.² report the results of a community-based survey assessing sexual activity and problems among 3005 men and women 57 to 85 years of age. Among participants with a spousal or other intimate relationship, the proportion who reported being sexually active decreased steadily across the age groups and was uniformly lower among women; in the subgroup of respondents who were 75 to 85 years of age, 38.5% of men and 16.7% of women reported sexual activity with a partner in the previous 12 months. With increasing age, women were also substantially less likely than men to be involved in an intimate relationship. Among both men and women who were sexually active, approximately half reported at least one bothersome sexual problem. The presence of chronic medical conditions was associated with reduced sexual activity and an increased frequency of sexual problems among both men and women, although it was not a sufficient explanation for the age-related decreases in sexual activity.

These findings are consistent with those of earlier studies³⁻⁵ showing decreases in sexual activity with increasing age, particularly in women. The present report has the advantages of having oversampled the oldest age group (persons who were 75 to 84 years of age at the time of screening) and having a relatively high survey response rate of 75%. However, it provides little information about older adults who are sexually inactive. Among these persons, 48% of respondents as

compared with only 5% of respondents who were sexually active considered sex as being "not at all important." Previous research has shown that older women are more likely than older men to lose interest in sex if they are not in a relationship.⁴ Unfortunately, the present study did not assess the proportion of respondents in a relationship who had become sexually inactive because of sexual problems, whether men or women had these sexual problems, and how the respondents felt about their relationship.

Most previous studies of the effect of aging on sexuality have involved either men or women, focusing on different factors in each case. Research in men has shown an inverse linear relationship between age and sexuality, even after adjustment for relevant age-related diseases. However, men differ considerably in terms of how quickly they age in this respect. In the Baltimore Longitudinal Aging Study in the 1970s, men who reported the highest frequency of sexual activity when they were younger had the slowest decline in sexual activity as they got older.⁶ This finding has been virtually ignored in more recent research, in which the principal focus has been on hormonal and vascular factors.

Testosterone acts on the male brain to promote sexual arousal and desire. With increasing age, there are varying degrees of reduction in both free testosterone⁷ and the number, and possibly responsiveness, of neurons in relevant areas of the brain such as the locus ceruleus, the brainstem center for testosterone-dependent arousal mechanisms. These changes contribute to the age-related decreases in sexual interest and, to some extent, erectile function.⁸ There are age-related changes in various aspects of the vascu-

lar and smooth-muscle tissues involved in the erectile process,⁸ including an increased sensitivity to inhibitory (i.e., contractile) signals in the erectile smooth muscle.⁹

The role of hormones in the effects of aging on women's sexuality remains less clear. The effect of menopause is complex, involving not only physiological changes (e.g., reduced vaginal lubrication related to a decrease in estrogen levels), but also an end to women's fertility, social attitudes about the role of postmenopausal women that vary across cultures, and a transitional phase with increased vulnerability to depression. The importance of menopause, as compared with other midlife factors, in explaining changes in sexuality has varied among studies.^{10,11}

Levels of testosterone in women gradually decrease with age, starting in the mid-30s, independently of menopause. This decrease may contribute to an age-related decrease in sexual interest among some women, as suggested by recent studies evaluating the effect of exogenous testosterone on sexual interest and response.¹² However, the relatively modest average increase in sexual interest and response reported in such studies is consistent with the varying responses of women to testosterone. Many women have a marked reduction in testosterone levels (e.g., with oral contraceptive use or after oophorectomy) without adverse effects on sexual function¹³; this may reflect genetic differences in women's responses to sex steroids.

As compared with studies in men, studies in women have emphasized the effect of relationship factors and mental health, which increasingly are proving to be more important predictors of sexual well-being than the physiological factors of sexual arousal and response.¹⁴ Relationship factors and mental health are likely to be as important as or more important than physiological factors as women age. Whereas many women report a decrease in their sexual interest and responsiveness as they progress through midlife, they are less likely to become distressed or worried about such changes as they get older. For many women, being in a relationship, the quality of that relationship, and a partner's sexual problems are more important than their sexual responsiveness.¹⁵ Women also differ with regard to what they find rewarding about sex. Some are motivated principally by the desire for intimacy, whereas for others the desire for sexual pleasure

and orgasm is equally important or even more important. These different motivational patterns may be affected in different ways by aging, although this remains to be shown.

Despite the high prevalence of sexual problems among the participants in the study by Lindau et al., only 38% of men and 22% of women reported having discussed sex with a doctor since the age of 50 years. Until recently, older adults tended to keep quiet about their sexuality because younger people assumed that they were not and should not be sexually active. Now the pendulum has swung, and the emphasis is increasingly on the sexuality of older adults and the provision of medical treatment to foster it.

Lindau et al. comment on a "massive and growing market" targeting older people. Perhaps a middle ground is preferable. For some older couples, sex can continue to play an important part in their relationship and well-being, and some may benefit from counseling or medication for that purpose. Other couples choose to leave sex behind as they settle into their later life. Often there may be the need for negotiation between partners. The medical profession should encourage older patients to feel comfortable in discussing sexual problems and in choosing whichever of these two options suits them best.

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1. Census 2000. Washington, DC: U.S. Census Bureau. (Accessed August 2, 2007, at <http://www.census.gov/main/www/cen2000.html>.)
2. Lindau ST, Schumm LP, Laumann EO, et al. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007;357:762-74.
3. Pfeiffer E, Davis GC. Determinants of sexual behavior in middle and old age. *J Am Geriatr Soc* 1972;20:151-8.
4. AARP/Modern Maturity Sexuality Study. Washington, DC: National Family Opinion Research, 1999.
5. Laumann EO, Nicolosi A, Glasser DB, et al. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res* 2005;17:39-57.
6. Martin CE. Factors affecting sexual functioning in 60-79-year-old married males. *Arch Sex Behav* 1981;10:399-420.
7. Vermeulen A. Androgen replacement therapy in the aging male — a critical evaluation. *J Clin Endocrinol Metab* 2001;86:2380-90.
8. Schiavi RC. *Aging and male sexuality*. Cambridge, England: Cambridge University Press, 1999.
9. Christ GJ, Schwartz CB, Stone BA, et al. Kinetic characteristics of alpha₁-adrenergic contractions in human corpus cavernosum smooth muscle. *Am J Physiol* 1992;263:H15-H19.
10. Dennerstein L, Alexander JL, Kotz K. The menopause and

sexual functioning: a review of population-based studies. *Annu Rev Sex Res* 2003;14:64-82.

11. Avis NE, Stellato R, Crawford S, Johannes C, Longcope C. Is there an association between menopause status and sexual functioning? *Menopause* 2000;7:297-309.

12. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause* 2006;13:770-9.

13. Bancroft J. The endocrinology of sexual arousal. *J Endocrinol* 2005;186:411-27.

14. Bancroft J, Loftus J, Long JS. Distress about sex: a national survey of women in heterosexual relationships. *Arch Sex Behav* 2003;32:193-208.

15. Hayes R, Dennerstein L. The impact of aging on sexual function and sexual dysfunction in women: a review of population based-studies. *J Sex Med* 2005;2:317-30.

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Understanding the Causes of Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a human disease resulting from the degeneration of motor neurons in the brain, spinal cord, and peripheral nervous system. The resultant clinical features include weakness of the arms, legs, and face and difficulties with speech, swallowing, and breathing. ALS affects women and men, regardless of ancestry, and the risk of disease increases with age. Its clinical progression is one of the fastest of the neurodegenerative diseases, with death (often from respiratory failure) typically occurring within 3 to 5 years after onset. The incidence is approximately 2 per 100,000 persons per year, and the prevalence is approximately 6 per 100,000 persons.¹

Generally speaking, the cause of ALS remains unknown. The most important advance in understanding the cause was provided through the identification of mutations in the *SOD1* gene (encoding copper-zinc superoxide dismutase) in about 2% of all patients and in 20% of those with an autosomal dominant form of ALS. The *SOD1* gene was found after many years of study; linkage studies of large families with autosomal dominant ALS ultimately proved pivotal in the discovery. Since then, mutations in five additional genes (encoding alsin, angiogenin, dynactin 1, senataxin, and vesicle-associated protein B) have been associated with a motor neuron disease (although often not a typical ALS phenotype) in a few families. There remain regions in the genome — genetic loci — that have been associated with disease but in which a specific gene has yet to be identified.²

Our understanding of the pathogenesis of ALS is also scant. A great deal of research has been done with the use of cellular and animal models, in particular with mice transgenic for the human *SOD1* mutations. These mice have some features that are similar to those of patients with ALS,

although a unifying understanding of any ALS mechanism remains elusive. Also disappointing is the lack of therapeutic advances built on findings from research in animals. Many therapeutic agents have been tested on mouse models of ALS, but they have so far failed to translate into clinical practice. The only disease-modifying medication for patients with ALS is riluzole, which was licensed more than 10 years ago. It was developed as an inhibitor of glutamate release with antiexcitotoxic effects, and in clinical trials its use has resulted in the extension of survival by approximately 2 to 3 months.³ A recent disappointment has been the trial of minocycline (a second-generation tetracycline with antiinflammatory properties); a preliminary report suggests that it may accelerate disease progression in humans,⁴ although it had promising effects on a mouse model transgenic for mutated *SOD1*.⁵

Although classic studies of linkage and mutation detection continue in the rare families in which the mutated gene has not been identified, clinical genetic studies have moved on from the “simple” genetics of clearly heritable mendelian disorders to the “complex” genetics of diseases that may have multiple genetic influences. This shift has been enabled by high-throughput methods, the cost of which — although considerable — is rapidly falling. At the center of many ongoing studies is the microarray (or “DNA chip”) designed to genotype hundreds of thousands of single-nucleotide polymorphisms (SNPs) simultaneously in a single experiment.⁶ SNPs are single-nucleotide variations in the DNA sequence that can be used as markers for neighboring genetic variation. By comparing the prevalence of a specific SNP in case patients and controls, one can determine whether the chromosomal region represented by the SNP is associated with disease.