den. Some feel that these data argue for aggressive and early detection programs among African-American men, although the outcome of treatment is still being evaluated.

Family history of prostate cancer is now a recognized risk factor for prostate cancer.The relative risk for a man developing it depends on the number of affected relatives (about 1.4 with one affected first degree relative and over 3 with more than one.) Current data suggest that familial prostate cancer may be a more aggressive type of cancer. Patients with familial prostate cancer have a worse outcome after radical prostatectomy than patients with nonfamilial prostate cancer. The poor result is primarily related to a higher distant relapse rate, suggesting that familial cancer is biologically more aggressive. Recent reports confirm the existence of a rare autosomal dominant prostate cancer susceptibility gene dubbed "HPC1" for "hereditary prostate cancer 1." Some feel these data argue for aggressive early screening for men with family history of prostate cancer, although outcome studies have not been completed.

In addition to the racial and familial risk factors associated with prostate cancer, several other risk factors are being hotly pursued, but are not established. Factors being evaluated include cigarette smoking and.consumption of dietary fat, tomatoes, and supplemental selenium. Other areas of interest include association with farming and history of vasectomy.

As cigarette smoking is implicated with lung cancer, it is also being investigated for its relationship with prostate cancer. Higher death rates from prostate cancer in current cigarette smokers suggesting that smoking may adversely affect survival in prostate cancer patients, however.

Dietary factors have been correlated with prostate cancer. Early studies support the hypothesis that high dietary fat intake is correlated with prostate cancer. Dietary fat intake was observed primarily with animal fat and meat consumption rather than vegetable fat consumption. Recent reports, however, tend to refute the previously asserted association, finding no link between dietary fat, especially animal sources, with risk or mortality of prostate cancer. Epidemiologic studies suggest high consumption of tomatoes or supplemental selenium may protect against prostate cancer. These findings need confirmation before dietary changes are made.

Recent reports indicate a positive correlation between prostate cancer and farming. Authors are speculate that hormonally active agricultural chemicals are potential risk factors among farmers.

The suggestion that vasectomy may increase the risk of prostate cancer is being disputed by evaluating confounding factors. For example, the odds ratio estimate for prostate cancer associated with vasectomy tended to increase among men with such known risk factors as father and brother with prostate cancer. Any increased risk may be related to detection bias or differential participation rates due to both vasectomy status and a family history of prostate cancer.

ANANIAS C. DIOKNO, MD
Royal Oak, Michigan

REFERENCES

Schaid DJ, Thibodeau SN, Blute ML, McDonnell SK. Genetic epidemiology of prostate cancer. J Urol 1997; 157(Suppl):53

Rodriguez C, Heath CW, Jr, Calle EE, Thun MJ, Tatham LM. Smoking and fatal prostate cancer in a large cohort of adult men. Am J Epidemiol 1997; 145:466–75

Veierod MB, Thelle DS, Laake P. Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. Int J Cancer 1997; 73:634–8

Clark LC, Dalkin BL, Krongrad A, Witherington R, Herlong JH, Carpenter HD. Decreased incidence of prostate cancer with selenium supplementation. J Urol 1997; 157 (Suppl):56 [Au: Please list up to 6 authors, then use et al.]

Keller-Byrne JE, Schaub EA, Khuder SA. Meta-analyses of prostate cancer and farming. Am J Ind Med 1997; 31:580–6

Zhu K, Weiss NS, Brawer MK, Stergachis A, McKnight B, Daling JR, Stanford JL.Vasectomy and prostate cancer: a case-controlled study in a health maintenance organization. Am J Epidemiol 1996; 144:717–22

Sildenafil: A Milestone in the Treatment of Impotence

WITH AN ESTIMATED 18–30 million American men who experience some degree of erectile dysfunction, it is not surprising that sildenafil, the first effective oral treament agent, released under the trade name Viagra by Pfizer Co. in April 1998, has been the fastest selling drug in pharmaceutical history. Sildenafil is an inhibitor of phosphodiesterase type 5 (PDE5). When initially investigated in patients with cardiac disease to promote vasodilatation, many reported improved erectile response.

Erections occur through sexual stimulation of the parasympathetic nervous system leading to release of the neurotransmitter nitric oxide, a powerful vasodilator derived from the endothelial cells lining the penile spaces—the corpus cavernosum. Nitric oxide then produces cyclic GMP which causes the smooth muscle of the corpus cavernosum to relax and fill with arterial blood, creating the erection. Pressure from these expanding spaces occludes veins against the tunica albugenia, surrounding the erectile tissue and leading to sustained erection.

Sildenafil works by blocking the enzyme, phosphodiesterase 5, which breaks down cyclic GMP, leading to higher sustained levels of cyclic GMP and relaxation of the smooth muscle spaces of the penis, and thereby amplifies sexual stimulation. Sildenafil has no direct effect on increasing libido but may enhance the sexual experience by decreasing performance anxiety caused by anticipated failure.

Available in 25, 50, and 100 milligram tablets,(a 50 mg tablet is the most common dose), sildenafil is taken about one hour prior to sexual activity to allow for absorption. Effects last 3–5 hours. About 70% of men with erectile dysfunction experience improved erections. Most side effects are attributable to vasodilatation: headache and flushing(10%). Additionally, about 3% of patients experience mild and transient visual effects—predominantly color tinge, but also light sensitivity—a pharmacological response thought to be related to sildenafil's weak inhibition of PDE6, found in the retina. The most serious side effect is hypotension, which may be amplified by concomitant use of nitrates, therefore, use with nitroglycerin or other nitrates is contradicted. Deaths reported to date in patients taking sildenafil do not appear to be greater than the same cohort

of cardiac patients not taking the drug. The Federal Drug Administration is investigating all reported deaths.

Sildenafil is not present in significant amounts in the ejaculate and it therefore poses no risk to conception or pregnancy in women whose partners take the drug.

Although with sildenafil oral pharmacotherapy becomes the front line treatment in the "goal-orientated" approach to to treatment, underlying medical conditions such as hypogondism, diabetes mellitus, and hypertension also need to be addressed in men with impotence.

What about women? Early reports suggest that sildenafil can increase lubrication and vascular vaginal engorgement in women, but safety and efficacy have not been established and sildenafil is not currently recommended for use in women. Several studies are underway, however.

Other drugs expected to be available shortly include phentol amine mesulate (Vaso-MaxTM by Zonagon Corp.), an apha-blocker reported to be effective in 40% of men by increasing penile arterial blood flow. In addition, a refined form of apomorphine delivered by sublingual administration will be available. Apomorphine does not affect cyclic GMP, but rather acts as a dopamine agonist, modulating erections through the nervous system. Early reports suggest a 50% effectiveness rate. Finally, research efforts will inevitably produce other phosphodiesterase inhibitors similar to sildenafil.

What about penile injections and the other forms of impotence treatment? The proven success of penile injection pharmacotherapy with agents such as prostaglandin E, and combinations as "tri-mix" (prostaglandin, papaverine and phentolamine) remains durable, and makes this approach still reasonable and cost effective. A difference in the mechanism of action of the injectables from sildenafil allows for success of these agents where sildenafil may fail. Intra-urethral insertion of prostaglandin E pellets (M.U.S.E by Vivus corp) remains an option for 10-20% of men. Yohimbine hydrochloride tablets (Yocon), 5.4 mg 3 times a day, are effective for 5–15 % of men.

Mechanical devices remain available in the form of the vacuum erection device and the surgically inserted penile prosthesis. It is currently unclear whether sildenafil will be an enhancement to these mechanical aids.

If medications, mechanical devices, or counseling are not effective, then referral to a urologist is appropriate.

DANIEL NACHTSHEIM, MD
La Jolla, California

REFERENCES

1. Boolell, M., Gepi-Attee S, Gingell JC, Allen MJ. Silenafil: a novel effective oral therapy for erectile dysfunction. Br J Urol 1996; 78: 257-261

2. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker, PA. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998; 338:1397–1404

ADVISORY PANEL TO THE SECTION ON UROLOGY