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## Why Study ED?

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I was recently at a Dr's appointment and the physician knew I did research for a living so asked me in what area. When I said erectile dysfunction, the physician laughed and made jokes as if this wasn't an important area of research. All too often this is still the reaction not only of non-scientists, but surprisingly of clinicians and other scientists as well. One of my own family members who is a physician asked me about my research and then quickly asked me to lower my voice to below a whisper when I said the word "penis". This kind of attitude is truly troubling and raises red flags about the way sexual medicine is viewed and supported in our culture.

Erectile dysfunction (ED) is a serious medical condition that affects ~50% of men between the ages of 40 and 70 [1]. The risk factors for ED include age, coronary artery disease, smoking, hypertension, dyslipidemia, peripheral vascular disease, higher body mass index, post radical prostatectomy/radiation therapy and diabetes. Current treatments include oral therapy with phosphodiesterase type (PDE5) inhibitors, injection with vasodilators and prosthesis implantation. Unfortunately these treatments are not effective in all ED populations, such as in prostate cancer and diabetic patients. A third of prostate cancer patients treated by radiotherapy and 30-70% of patients treated by radical prostatectomy experience ED, depending on the extent of nerve sparing during surgery [2-3]. Although potency improves with time post prostatectomy, ED is common 5 years following radical prostatectomy [4-5]. Current treatments for ED are 50-60% ineffective in prostatectomy patients [2-3].

Diabetic men have impotence at an earlier age, are 2.1 times more likely to develop ED (Massachusetts Male Aging Study) and the incidence of ED may range as high as 75% [6]. Diabetes is expected to affect 366 million patients by the year 2030 [7] and current treatment strategies are ineffective in 56-59% of diabetic patients [8]. The reduced efficacy of treatments makes novel therapeutic approaches to treat and prevent ED essential.

ED has recently been identified as a marker for silent coronary artery disease with a lead-time of 2-3 years between moderate to severe ED diagnosis and vascular disease presentation [1]. Thus ED diagnosis and treatment may have long lasting consequences on male health. Many people have the misconception that ED only affects aging men or those with health concerns. However ED also affects 22% of men under the age of 40 [9]. When considering the significance of ED, it must be taken into account that ED not only affects impotent men but also their partners. Two studies highlight the significance of quality of life to the affected patients. A study of diabetic impotent patients showed that men were willing to pay more to treat their ED than all other complication of diabetes except for blindness and renal failure [10]. Another study in men, who were electing treatment for localized prostate cancer, showed that the primary concern in 45% of the patients was quality of life after treatment [11]. Thus for those who are affected, quality of life is a highly significant issue.

Two of the underlying causes of ED are vascular insufficiency and injury to the cavernous nerve (CN), which provides innervation to the penis. The CN frequently undergoes resection, crush and tension injury during prostatectomy surgery, resulting in ED. Radiation treatment for

prostate cancer also damages the CN, as does peripheral neuropathy in diabetic patients and aging related loss of neurons. Although peripheral nerves have a limited ability to regenerate, a return of erectile function typically does not occur due to irreversible downstream morphological changes in the penis. Tissues innervated by the damaged nerve have deteriorating function, morphological remodeling including induction of smooth muscle apoptosis [12] and fibrosis [13], which affects the responsiveness of penile smooth muscle. Smooth muscle dysfunction resulting from CN injury makes traditional therapies such as PDE5 inhibitors less effective. Thus new treatments that address both the downstream morphological changes in the penis and the underlying cause of the dysfunction, injury to the CN, are necessary.

As is the case with other peripheral nerves, efforts to regenerate the CN have so far had only limited success in animal models, and have not yet resulted in improved clinical therapies. Study of the CN and its regeneration can lead to insights that are widely applicable to regeneration of other peripheral nerves. Study of smooth muscle and endothelial dysfunction, common in ED patients, has led to useful insights for understanding the underlying mechanisms of how cardiovascular disease develops. Thus study of ED and development of improved treatment strategies may not only impact sexual function, but may also have a broader influence in disease treatment.

We've come a long way since I first started studying urogenital development and erectile dysfunction eighteen years ago. It used to be that the audience was primarily men who would look uncomfortable at the discussion of erectile dysfunction. Now when I attend the Sexual Medicine Society meetings the audience has changed to include a healthy balance of men and women and the study of sexual function has become an established and significant area of research. However continuing effort is required to educate the public, to raise awareness of funding agencies and to change public health policy to increase the priority of ED research and funding, which is sorely under represented in current NIH policy.

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