Endocrine, *vol. 23, nos. 2–3, 119–123, March–April 2004* 0969–711X/04/23:119–123/$25.00

Causes of Erectile Dysfunction

Jeremy P. W. Heaton and Michael A. Adams

Departments of Urology and Pharmacology and Toxicology, Queen's University, 76 Stuart Street, Kingston, Ontario, Canada

Erectile dysfunction (ED) arises as a result of a collision of circumstances among any of a number of factors (e.g., risk factors, causes, probable associations), each with its own primary power to affect the outcome. Furthermore, each of the components has its own timing as part of a complex effort of compensation and adjustment that often obscures the individual details. In the end, ED results from a failure of local tissues or systemic supply and control structures. The power of any individual "cause" to degrade erectile function is an important but as-yet unquantified property. The power of a small abnormality over a long or critical period (e.g., organogenesis), or many small contributions, or multiple risk factors will certainly be greater than the sum of the individual elements. Without a full quantitation of pathways and their potential influence, one can compare the importance of causative factors only in limited ways. Not surprisingly, it is the presence of a multiplicity of unidentified or poorly understood causative factors that accounts in large measure for the current inability to cure and prevent ED. There are two other important properties of a putatively causative factor for ED—reversibility and preventability—and these are strongly influenced by the time of onset and the duration of impact. Thus, a critical understanding that comes from recognizing the importance of the temporal associations of component factors is that the causes of ED in an individual may be guessed at but cannot be fully disclosed by an analysis of a "snapshot" of the disease taken at the time of diagnosis.

Key Words: Erectile dysfunction; risk factor; faulty erectile functions.

Introduction

A consideration of the causes of erectile dysfunction (ED) can be made from several vantage points. The articles in this symposium issue provide detailed insight into the issues of causality. Epidemiologic information builds a picture of factors relevant to and associated with ED. A study of the biochemistry of erections provides a complex picture of pathways that can potentially fail and contribute to ED. A discussion of the physiology of erection will reveal mechanisms and structures that can develop faults leading to ED. Endocrine pathways that modulate sexual function may cause ED. Clinical, social, and psychosexual problems, some of which could be revealed during evaluation of a patient, may contribute to ED. Cardiovascular factors can clearly create clinical consequences for erectile function when they deviate from the appropriate normal range. Therefore, cardiovascular disease and ED frequently coexist.

However, when looking for cause of a complex dysfunction (ED) in an integrated system (man) it will seldom be singular. Even a healthy young man undergoing radical prostate surgery has age, subclinical vascular deterioration, and the burden of anxiety about cancer and cancer surgery to add to the physical injury of surgery, all of which are potentially at least additive causes of ED. The range of possibilities represented by the catalog of psychophysiologic mechanisms detailed in this symposium is huge. It is no longer credible to assign as a causative categorization the designations *organic, psychogenic*, or *mixed (1).* These terms have defied precise definition while allowing the accumulation of a necessary body of clinical and basic understanding. Although we currently have the potential for an encyclopedic understanding of potential causative factors, only a few of them will stand out as important since therapies still largely treat the symptom (the soft penis) regardless of proximate cause *(2)*. Put another way, although sildenafil is able to treat a significant number of patients, it would be overly simplistic to describe pharmacologic correction of the condition as cure of the cause. In fact, treatment success provides a direct measure of the power/capacity of the particular pathway cyclic guanosine 5'-monophosphate in that regardless of the fault itself and up to a point nonspecific amplification of a proerectile signal can overcome the impact of many faults. In looking at causes of ED, there is a need to observe that there is a limited benefit at present from understanding them. Reversible causes are, to be brutally realistic, ignored by patients just as they are if lung cancer and heart disease, rather than ED, are the potentially avoidable consequences. For example, "everyone knows" that smoking is bad for erections, governments warn about ED on cigarette packages, and yet documenta-

Received September 15, 2003; Revised November 14, 2003; Accepted November 14, 2003.

Author to whom all correspondence and reprint requests should be addressed: Dr. Jeremy P. W. Heaton, 76 Stuart Street, Kingston, Ontario, Canada K7L 2V7. E-mail: heatonj@post.queensu.ca

Table 1
Links Among Possible Etiologic Factors and ED

1. Suspected (e.g., smoking *[4]*)
2. Associated (e.g., inactivity *[5]*)
3. Contributory cause (e.g., hypertension *[6]*)
4. Cause (e.g., aortoiliac occlusion *[7]*)

tion of an unbroken thread of fact that links ED with smoking is a surprising challenge *(3)*.

There is a need to understand the different status of cause and association. There is a need to recognize the many factors that contribute even in a small way to a decline in erectile function. The evidence for contribution, association, or causality for any one factor may be difficult to obtain despite the intuitive appeal (Table 1). Many of the possible contributory causes can be thought of as risk factors. Overall, the least judgmental way to express the "issues" relevant to a loss of erections is as cofactors or comorbidities. In fact, the "issues" can be shown to exist in the same host as the ED and may in certain circumstances be causally linked to the ED.

Mechanistic Basis for ED

In mechanistic terms, ED is the failure of penile tissues to respond to an appropriate sexual signal. The classic definition of ED (the consistent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance *[8]*) has been parsed many times, and it is clear that there is some homology with female sexual dysfunction, and a justifiable desire to emphasize parallels. The particulars of ED accentuate the neurovascular events resulting in penile erection.

In the following, the concept of cause should be taken to mean the general ability of a fault to degrade erections to some extent. The pathway that can contain the fault has a normal role in the complex of mechanisms that create an erection. Each pathway has associated with it a *gain,* i.e., the overall capacity of a signal to induce a change. This capacity to influence the outcome can also be viewed as the power of a pathway to influence the final erectile outcome. Furthermore, it is important to recognize that the loss of function in any one pathway will inevitably result in compensatory changes in other pathways and that the sum total of the consequent changes resulting from the single original fault may exceed the known power or *gain* of the original pathway (e.g., a single partial obstruction of a renal artery eventually causes a degree of hypertension that is way out of proportion to the stenosis-induced increase in resistance and the increased rennin *[9]*). Thus, any individual fault in a pathway may have an influence on the usual stimulus-response relationship of the penis. The fault may be partial or total, and yet the influence that an individual fault may have on the end point of erection may not be clinically evident on its own. However, as with all complex physiologic systems, subclinical faults in individual subsystems may add to or synergize with other faults, resulting in a clinical reduction in erectile function. For example, a small amount of a α-adrenergic signal (a model for anxiety) that produces no blood pressure (BP) change by itself plus a small amount of endothelin (equivalent to the effects of smoking, hypertension, or dyslipidemia) that also produces no BP change by itself will when combined produce substantial increases in BP *(10)*.

The power of any individual cause, therefore, to degrade erectile function is an important but as-yet unquantified property. The power of a small contribution over a long or critical period (e.g., organogenesis), many small contributions, or multiple risk factors will certainly be greater than the sum of the individual elements. Without a full quantitation of pathways and their potential influence, researchers can compare the importance of causative factors only in limited ways: usually researchers fall back on epidemiologic data and then can only compare factors that are currently clinically evident and measurable. It is the presence of a multiplicity of unidentified or poorly understood causative factors that accounts in large measure for the current inability to cure and prevent ED.

There are two other important properties of a putatively causative factor for ED—reversibility and preventability—and these are strongly influenced by the time of onset and the duration of impact. Thus, a critical understanding that comes from recognizing the importance of the temporal associations of component factors is that the causes of ED in an individual may be conjectured but cannot be fully disclosed by an analysis of a "snapshot" of the disease taken at the time of diagnosis. Take, e.g., the case of a man with early onset of hypertension that lasts for 10 yr before it is recognized and treated. Five years later the man may be normotensive taking minimal or no medication and experiencing moderate ED. The damage done by the hypertension is real at the level of the penis but clinically, as yet, unapparent.

The causes of ED can be dichotomized into local and systemic problems. Local problems are the anatomic, cellular, biochemical, proteomic, genomic, and other properties

Table 2
Potential Causes of ED from Local Factors:
Penile Arteriolar Dilation, Penile Sinusoidal Dilation, and Penile Efferent Venous Occlusion

System affected	Example	Power	Reversibility	Preventability
Vascular smooth muscle *(18)*	Age *(19)*	High	None	None
	Diabetes *(20)*	High	Limited	Moderate
	Obesity	High	High	High
Endothelial cell *(21,22)*	Smoking *(23,24)*	High	Limited *(28)*	High
	Diabetes *(25)*	High	Limited	Moderate
	Hypertension *(26)*	Moderate	High	High
	Dyslipidemia *(27)*	Moderate	Moderate	High
Vascular lumen *(29)*	Atherosclerosis *(30)*	High	Limited	High
	Hypertension *(31)*	High	Moderate	High
Stromal cells *(32)*	Age	High	None	None
	Diabetes	High	Limited	Moderate
	Peyronie disease *(33)*	Moderate	Limited	Unknown
Intrapenile neural network *(34)*	Diabetes	Moderate	Limited	Moderate
Gap junctions *(35)*	Diabetes	Moderate	Limited	Moderate

Table 3
Potential Causes of ED from Cellular Factors:
Penile Arteriolar Dilation, Penile Sinusoidal Dilation, and Penile Efferent Venous Occlusion[a]

System affected	Example	Power	Reversibility	Preventability
Nitric oxide mechanisms *(36,37)*	cGMP	High	High—inhibit T5 phosphodiesterase *(38)*	Moderate
Other vasodilator mechanisms *(39)*	cAMP	High	High—PGE_1	Moderate
Vasoconstrictor mechanisms *(40)*	Adrenergic	High	Moderate–high	Moderate
	Endothelin *(41)*	Moderate	High	Moderate
	Angiotensin	Moderate	High	Moderate
Metabolic	Hypoxia	High	Duration dependent	By cause
	Hypogonadism	High	High	High
	O_2-free radicals *(42)*	Moderate	Moderate	Moderate
Ion channels	Potassium	Moderate	Low	Low
	Calcium	Moderate	Low	Low

[a]Therapeutic strategies that tie in to the systems identified may take the form of agonists, antagonists, genomics, proteomics, and so on. For example, the manipulation of ion channels by gene transfection is another way to treat ED using a strategy based on ion channels. CGMP, cyclic guanosine 5'-monophosphate; cAMP, cyclic adenosine monophosphate.

of the penis itself (Tables 2 and 3). Systemic problems are the supply and control factors that lie external to the penis and on which aspects of penile function depend (Table 4). The most common, and long-established, concept of cause of ED places vascular disease in the penis as the critical factor *(11)*, and this has more recently become linked with the probability of associated systemic cardiovascular disease *(12)*. The importance of this view has been reinforced by the dramatic ability of suitable phosphodiesterase inhibitors to improve erectile function *(13)*. Of the systemic factors that have clearly been found to be causative for ED, castration *(14)* and age *(15)* are the most established. Less well defined but of great importance is failure of centrally derived neural signals to overcome a natural or an enhanced state of inhibition *(16)*. The result is that the erectile stimulus is insufficient to derive a maximum response from the penile tissue *(17)*. There is a much less concrete understanding of the central nervous system (CNS) disease processes that underlie this fundamental and common cause and cofactor, despite its importance, and because of its complexity.

Conclusion

ED arises as a result of a collision of many factors, each with its own primary power to affect the outcome, each with its own timing, and each a part of a complex effort of compensation and adjustment that obscures the details. ED

Table 4
Potential Causes of ED from Systemic Factors: Proerectile (Vasodilator) Signaling to Increase, Erectolytic (Vasoconstrictor) Signaling to Decrease, Pre-penile Vasculature to Dilate, Cardiac Response, BP, Oxygenation, and Hormonal Milieu

System affected	Example	Power	Reversibility	Preventability
CNS *(43)*	Depression *(44)*	High	Moderate	Moderate
	Negative imagery	Moderate	Low	Low
	Stress/anxiety	High	Moderate	Low
Midbrain *(45)*	Vasomotor crisis	High	High	High
	Parkinson disease	High	Low	Low
Spinal cord	Aging	High	Moderate–low	Low
Peripheral nerves	Prostatectomy nerve injury	High	Low	Moderate
	Sensory *(46)*	Moderate	Low	Moderate
Cardiorespiratory	Congestive heart failure	High	Moderate	Moderate
	Myocardial infarction	High	High	High
Lifestyle issues	Obesity *(47)*	Moderate	Moderate	High
	Inactivity	Moderate	High	High
Peripheral vascular	Aortoiliac disease	High	Low	Moderate
	Pelvic trauma/arterial lesion	High	High	Low/moderate
Autonomic	Anxiety/stress	High	Potentially high	Potentially high
Endocrine	Diabetes	High	Limited	Moderate
	Hypogonadism *(48)*	High	High	Limited
	Hyperprolactinemia *(49)*	High	High	Limited
Metabolic	Hypoxia	High	Time dependent	Low
Toxic/drug effects	Antihypertensives *(50)*	High	High	High

results from a failure of local tissues or systemic supply and control structures. As clinicians and scientists, we identify multifactorial vascular dysfunction, associated with systemic vascular disease, as a common cause of ED that is mostly remediable by overwhelming one powerful pathway. We acknowledge that the exact origins of the vascular dysfunction are both complex and largely unknowable. We can see that there is an overriding role for the incoming signal to the penis to modulate any therapy short of a prosthesis but, at present, we have only a hazy understanding of the important CNS changes that also substantially impact erectile function.

References

1 Sachs, B. D. (2003). *Int. J. Impot. Res.* **15(1),** 72–78.
2 Andersson, K. E. (2001). *Pharmacol. Rev.* **53(3),** 417–450.
3 McVary, K. T., Carrier, S., and Wessells, H. (2001). *J. Urol.* **166(5),** 1624–1632.
4 Nicolosi, A., Moreira, E. D. Jr., Shirai, M., Bin Mohd Tambi, M. I., and Glasser, D. B. (2003). *Urology* **61(1),** 201–206.
5 Johannes, C. B., Araujo, A. B., Feldman, H. A., Derby, C. A., Kleinman, K. P., and McKinlay, J. B. (2000). *J. Urol.* **163(2),** 460–463.
6 Hale, T. M., Okabe, H., Bushfield, T. L., Heaton, J. P., and Adams, M. A. (2002). *J. Urol.* **168(1),** 348–354.
7 Cormio, L., Edgren, J., Lepantalo, M., et al. (1996). *Eur. J. Vasc. Endovasc. Surg.* **11(4),** 453–457.
8. Jardin, A., Wagner, G., Giuliano, F., Padma-Nathan, H., and Rosen, R. (eds.) (2000).
9 Korner, P. I. (1995). *J. Hypertens.* **13(12 Pt. 2),** 1508–1521.
10 Adams, M. A., Banting, J. D., Maurice, D. H., Morales, A., and Heaton, J. P. (1997). *Int. J. Impot. Res.* **9(2),** 85–91.
11 Ruzbarsky, V. and Michal, V. (1977). *Invest. Urol.* **15(3),** 194–199.
12 Solomon, H., Man, J. W., and Jackson, G. (2003). *Heart* **89(3),** 251–253.
13. Kuthe, A., Montorsi, F., Andersson, K. E., and Stief, C. G. (2002). *Curr. Opin. Investig. Drugs* **3(10),** 1489–1495.
14 Marumo, K., Baba, S., and Murai, M. (1999). *Int. J. Urol.* **6(1),** 19–23.
15 Feldman, H. A., Goldstein, I., Hatzichristou, D. G., Krane, R. J., and McKinlay, J. B. (1994). *J. Urol.* **151(1),** 54–61.
16 Bancroft, J. and Janssen, E. (2000). *Neurosci. Biobehav. Rev.* **24(5),** 571–579.
17 Andersson, K. E. (2000). *Int. J. Impot. Res.* **12(Suppl. 4),** S26–S33.
18 Wespes, E. (2002). *Int. J. Impot. Res.* **14(Suppl. 1),** S17–S21.
19 Bakircioglu, M. E., Sievert, K. D., Nunes, L., Lau, A., Lin, C. S., and Lue, T. F. (2001). *J. Urol.* **166(2),** 734–738.
20 Cartledge, J. J., Eardley, I., and Morrison, J. F. (2001). *BJU Int.* **87(4),** 402–407.
21 Maas, R., Schwedhelm, E., Albsmeier, J., and Boger, R. H. (2002). *Vasc. Med.* **7(3),** 213–225.
22 Choy, J. C., Granville, D. J., Hunt, D. W., and McManus, B. M. (2001). *J. Mol. Cell. Cardiol.* **33(9),** 1673–1690.
23 Lehr, H. A. (2000). *Microcirculation* **7(6 Pt 1),** 367–384.
24. Michael Pittilo, R. (2000). *Int. J. Exp. Pathol.* **81(4),** 219–230.
25 Guerci, B., Kearney-Schwartz, A., Bohme, P., Zannad, F., and Drouin, P. (2001). *Diabetes Metab.* **27(4 Pt. 1),** 425–434.
26 Schiffrin, E. L. (2002). *Am. J. Hypertens.* **15(10 Pt. 2),** 115S–122S.
27 Kita, T., Kume, N., Minami, M., et al. (2001). *Ann. NY Acad. Sci.* **947,** 199–205.

28 Jeremy, J. Y. and Mikhailidis, D. P. (1998). *J. R. Soc. Health* **118(3),** 151–155.
29 Kunz, J. (2000). *Gerontology* **46(6),** 295–299.
30 Behr-Roussel, D., Bernabe, J., Compagnie, S., et al. (2002). *Atherosclerosis* **162(2),** 355–362.
31 Hale, T. M., Okabe, H., Bushfield, T. L., Heaton, J. P., and Adams, M. A. (2002). *J. Urol.* **168(1),** 348–354.
32 Sattar, A. A., Wespes, E., and Schulman, C. C. (1994). *Eur. Urol.* **25(2),** 142–144.
33 Gonzalez-Cadavid, N. F., Magee, T. R., Ferrini, M., Qian, A., Vernet, D., and Rajfer, J. (2002). *Int. J. Impot. Res.* **14(5),** 361–374.
34 Stief, C. G., Noack, T., and Andersson, K. E. (1997). *World J. Urol.* **15(1),** 27–31.
35 Melman, A. and Christ, G. J. (2002). *Urol. Clin. North Am.* **28(2),** 217–231.
36 Burnett, A. L. (2002). *J. Androl.* **23(5),** S20–S26.
37 Albrecht, E. W., Stegeman, C. A., Heeringa, P., Henning, R. H., and van Goor, H. (2003). *J. Pathol.* **199(1),** 8–17.
38 Corbin, J. D., Francis, S. H., and Webb, D. J. (2002). *Urology* **60(2 Suppl. 2),** 4–11.
39 Saenz de Tejada, I. (2002). *Int. J. Impot. Res.* **14(Suppl. 1),** S6–S10.
40 Mills, T. M., Chitaley, K., and Lewis, R. W. (2001). *Int. J. Impot. Res.* **13(Suppl. 5),** S29–S34.
41 Maas, R., Schwedhelm, E., Albsmeier, J., and Boger, R. H. (2002). *Vasc. Med.* **7(3),** 213–225.
42 Jones, R. W., Rees, R. W., Minhas, S., Ralph, D., Persad, R. A., and Jeremy, J. Y. (2002). *Expert Opin. Pharmacother.* **3(7),** 889–897.
43 Allard, J. and Giuliano, F. (2001). *Curr. Urol. Rep.* **2(6),** 488–494.
44 Shabsigh, R., Zakaria, L., Anastasiadis, A. G., and Seidman, A. S. (2001). *Curr. Urol. Rep.* **2(6),** 463–467.
45 McKenna, K. E. (1999). *Annu. Rev. Sex. Res.* **10,** 157–183.
46 Bleustein, C. B., Arezzo, J. C., Eckholdt, H., and Melman, A. (2002). *Int. J. Impot. Res.* **14(6),** 433–439.
47 Derby, C. A., Mohr, B. A., Goldstein, I., Feldman, H. A., Johannes, C. B., and McKinlay, J. B. (2000). *Urology* **56(2),** 302–306.
48 Heaton, J. P. and Morales, A. (2003). *Urol. Clin. North Am.* **30(1),** 73–81.
49 De Rosa, M., Zarrilli, S., Di Sarno, A., et al. (2003). *Endocrine* **20(1-2),** 75–82.
50. Grimm, R. H. Jr., Grandits, G. A., Prineas, R. J., et al. (1997). *Hypertension* **29(1 Pt. 1),** 8–14.