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Pathophysiology of erectile dysfunction

IAN EARDLEY

Abstract

New knowledge regarding the importance of vascular, endocrine, cellular, neural and psychological mechanisms in the pathophysiology of erectile dysfunction has led to changes in the theories of causation. Additionally several drugs can impair sexual function. These topics are reviewed herein.

Key words: pathophysiology, diabetes, risk factors, erectile dysfunction.

Introduction

From a historical perspective, theories pertaining to the pathophysiology of erectile dysfunction (ED) have changed as time has gone by. In the 1960s, the prevailing wisdom was that most ED had a psychogenic origin, and it was only in the second half of the 20th century, as we have gained increasing knowledge of the physiology of normal erectile function, that we have begun to understand the importance of vascular, endocrine, cellular and neural mechanisms in the development of ED. Even now our knowledge is incomplete, largely because of our continuing ignorance of many of the central mechanisms that are involved in the control of erection, and consequently of the central causes of ED. We know that the psyche can have a considerable effect upon penile erection, and we know that psychogenic factors impinge upon the pathophysiology of ED in almost all men, but quite how this occurs at a neural or organisational level is, as yet, unclear.

One other general point that is worth making, is that for most men, there are several aetiological factors involved in the development of their ED. An example of this is the ED that accompanies aging, where vascular, endocrine, cellular, degenerative, psychological and neural factors may all contribute to an individual's erectile difficulties.

There are several ways of classifying the pathophysiological causes of ED, but the classification used in this article is shown in table 1. A full understanding of the ways in which disease can interfere with erection can only be seen if there is at least some



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Table 1. A classification of the causes of erectile dysfunction

- | | |
|---------------|--------------|
| ● Psychogenic | ● Vascular |
| ● Neural | ● Cellular |
| ● Endocrine | ● Iatrogenic |

understanding of the normal physiology of an erection and accordingly this review will commence with a short description of the more salient features of penile erection.

Physiology of penile erection

Stimuli that can lead to penile erection include tactile stimuli to the penis and genitalia which will produce a reflex erection, while erotic stimuli, whether visual, auditory, olfactory or imaginative also produce penile erection by a mechanism which involves the paraventricular nucleus and medial preoptic area of the hypothalamus. A third mechanism is involved in the production of nocturnal erections that occur in all men during REM sleep. While the exact central pathways involved in these processes are unclear, descending pathways from the hypothalamus ultimately lead to increased parasympathetic and decreased sympathetic neural activity within the penis. The parasympathetic nerves release a number of neurotransmitters within the penile tissue, of which the most important is nitric oxide (NO). However, the neural release of

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Table 2. Predisposing, precipitating and maintaining factors

Predisposing factors	Educational issues (e.g. poor sexual education) Cultural issues (e.g. restricted upbringing) Traumatic sexual experience Lifestyle issues (e.g. marital, financial stress)
Precipitating factors	Organic disorders Extra-marital affairs Unreasonable expectations Depression and anxiety Loss of partner (e.g. 'Widower's syndrome')
Maintaining factors	Performance related anxiety Diminished attraction to partner Educational issues (e.g. poor sexual education) Fear of intimacy

NO is supplemented by release from the vascular endothelium and this leads to relaxation of the smooth muscle in the penile arteries and in the spongy tissue of the corpora cavernosa. As a result of this, there is arterial dilatation, cavernosal relaxation and increased pooling of blood within the trabecular spaces of the corpora. As a consequence, the veins which normally carry blood out of the penis are compressed against the tunica albuginea, leading to reduced venous outflow, and this so-called 'veno-occlusive' mechanism results in the rigid penile erection.

Even this brief description of the physiology of penile erection highlights a number of sites where disease could conceivably interfere with the erectile process, such as the nervous system (both centrally and peripherally), the arterial system, the vascular endothelium and the penile smooth muscle. In addition, we know that a variety of endocrinological abnormalities can also affect this process at a number of different levels, as can a wide range of both therapeutic and recreational drugs.

Psychogenic erectile dysfunction

Psychogenic issues are involved in almost all men with ED, even if we now know that in the majority of men the dominant pathophysiological processes are organic. Such is the central importance of penile erection to the male psyche, that even the most minor organic malfunction can result in psychological consequences, which can progress to so-called 'performance related anxiety'. In fact, a variety of factors can contribute to psychogenic ED, and these can be conveniently divided into three groups, predisposing, precipitating and maintaining factors. Examples of each of these are shown in table 2.

One of the clinical features that suggests a significant psychogenic component in a man's ED is the presence of normal nocturnal erections. If they are present and normal, then it is likely that the neural, vascular and endocrine mechanisms that are intrinsic to normal penile erection are all intact, and there is a predominant psychogenic component to the pathophysiology of the ED.

Neurogenic erectile dysfunction

Diseases of both the central and the peripheral nervous system

Table 3. Neurogenic causes of erectile dysfunction

Diseases of the central nervous system	Multiple sclerosis Spinal cord injury Depression Parkinson's disease Cerebrovascular disease
Diseases of the peripheral nervous system	Cauda equine compression Prolapsed inter-vertebral disc Peripheral neuropathy (e.g. diabetes, alcohol) Surgical injury to pelvic nerves

can result in erectile dysfunction. Again, there are too many to allow much detailed discussion and a list of the commoner neurogenic causes of ED is given in table 3.

Several psychiatric conditions, such as depression, can result in ED, and they are more usefully considered as organic causes rather than psychogenic. In fact, the relationship between depression and ED is a complex one. Depression can certainly result in ED, but mild depression can also result from ED, such that it has become clear that treatment of ED in men with mild depression can improve the depressive symptoms as well as the ED.¹ A further issue is the sexual effect of the drugs used to treat depression (see later).

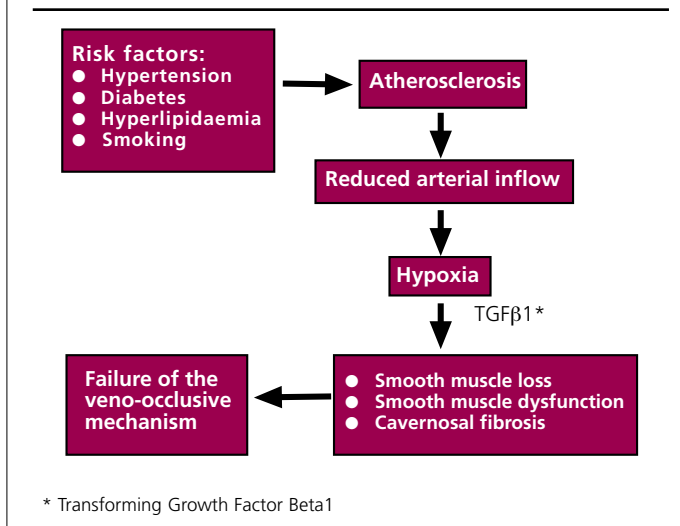
Spinal cord injury affects erectile function, but the picture depends upon the level and extent of the injury. Broadly speaking, men with high lesions can still get reflex erections (via intact reflex pathways) while men with low cord lesions can sometimes continue to get psychogenic erections (via intact sympathetic pathways).

Other issues that are relevant in men with neurological disease are the effects of the disease upon mobility, manual dexterity and urinary function. Disorders of one or all of these systems might also exacerbate any erectile dysfunction. Nowhere is this seen more clearly than in multiple sclerosis, where quite severe disability can be seen in young men who might have relatively normal sexual function. Furthermore, even if erectile function has been lost, but can be restored by treatment, other disabilities might preclude sexual activity.

Endocrine mechanisms of erectile dysfunction

Testosterone is central to normal male sexual function having an important role in both sexual drive and penile erection. However, a reduced level of testosterone has variable effects upon sexual function. There is reduction in libido, but a less marked effect upon erectile function. Men who are hypogonadal do not necessarily lose psychogenic and reflex erections. They do, however, have diminished nocturnal erectile activity, with both reduced duration and rigidity of the erection.

Again, there is a large number of causes of reduced serum testosterone, but they can be broadly classified into primary hypogonadism (where the disease is testicular) and hypogonadotropic hypogonadism, where the primary disease affects the pituitary or the hypothalamus. Examples of the former are the

Figure 1. Cellular mechanisms in the pathophysiology of erectile dysfunction

hypogonadism which may follow mumps orchitis, or that which follows radiotherapy to the testes. Examples of the latter include congenital causes such as Kalmann's syndrome and acquired causes such as pituitary tumours.

A rare endocrine cause of ED is a prolactin secreting tumour of the pituitary. The presenting symptoms are typically ED, galactorrhea and gynaecomastia. The serum testosterone is usually reduced and the diagnosis is made by CT scanning of the pituitary.

Vasculogenic erectile dysfunction

Vascular disease is probably the most common cause of ED, and of all the vascular causes, the commonest is atherosclerosis. However, not only is atherosclerosis associated with ED, but its risk factors, namely smoking, hypertension, hyperlipidaemia and diabetes, are also associated with the development of ED. The Massachusetts Male Aging study described an association between ED and hypertension, diabetes and hypercholesterolaemia.^{2,3} The Cologne study of men with ED also confirmed an association between ED and diabetes and hypertension,⁴ while several studies have demonstrated an association between smoking and ED.⁵ At a cellular level, it has been suggested that a reduced arterial inflow leads to relative hypoxia within the penis with subsequent cellular effects (figure 1). The crucial cellular mediator appears to be Transforming Growth Factor Beta 1 (TGFβ1), which is increased in hypoxia and induces trophic changes in the cavernosal smooth muscle.

In addition to atherosclerosis, other disorders of both the arterial supply and the venous drainage of the penis can result in ED, and examples of both are shown in table 4.

When there is failure of the veno-occlusive mechanism, the phenomenon of venous leakage occurs. This is a purely radiological phenomenon seen during specialised radiological imaging of the penis (cavernosography). When originally described, it was thought that the abnormal veins represented the primary patho-

Table 4. Vascular causes of erectile dysfunction

Type of condition	Examples
Arterial disorders	Pelvic fracture associated arterial injury Radiotherapy to pelvic malignancy Aorto-iliac surgery
Abnormal venous channels	Primary (congenital) Following surgery for priapism Following repeated urethral surgery
Failure of veno-occlusive mechanism	Abnormal tunical function (e.g. due to aging, Peyronie's) Reduced or abnormal smooth muscle (e.g. due to aging, renal failure)

logical abnormality, and for some years surgical ligation of these veins was undertaken as a means of treating ED. However, with the understanding that the venous leak was almost always secondary to abnormalities of the tunica albuginea or to disease of the cavernosal smooth muscle (and with the realisation that the results of venous surgery were poor), surgical treatment has almost completely disappeared.

Cellular causes of erectile dysfunction

Two types of cavernosal cells are central to penile erection; namely smooth muscle cells and endothelial cells. The vascular endothelial cells line the trabecular spaces of the cavernosal sinusoids and release a variety of vasoactive chemicals which control smooth muscle tone within the penis. The most important of these is NO. Diseases which damage the endothelium impair the vascular response of the penis to neural stimuli. A number of diseases damage the endothelium, including hypercholesterolaemia, but the most important is diabetes mellitus (See figure 2a and b).

The structural changes in the endothelium that are produced by diabetes are accompanied by functional changes that result in impaired smooth muscle relaxation.^{6,7}

The diseases of smooth muscle that can result in erectile dysfunction have already been alluded to above. Aging results in reduced penile smooth muscle, as does atherosclerosis, while renal failure results in smooth muscle dysfunction. When the smooth muscle malfunctions, arterial dilatation is incomplete, cavernosal relaxation fails to occur and the veno-occlusive mechanism fails.

Iatrogenic erectile dysfunction

A large number of drugs can impair sexual function, either by an effect upon erectile function, ejaculatory function or sex drive. Some of the more commonly used drugs are listed in table 5. Use of these drugs very rarely produces ED on their own, their action usually being an adjunct to another pathophysiological mechanism.

The sexual effects of recreational drugs are shown in table 6.

Surgery and radiotherapy can also impair erectile function. The commonest surgical cause of ED is radical pelvic surgery for rectal cancer, bladder cancer or prostate cancer. The parasympa-

Figure 2. Electron micrographs of (a) normal penile vascular endothelium and (b) the effect of diabetes in the rabbit (Micrographs courtesy of Mr M Sullivan). Note the ragged appearance of the endothelium and the deposition of red and white blood cells in diabetes.

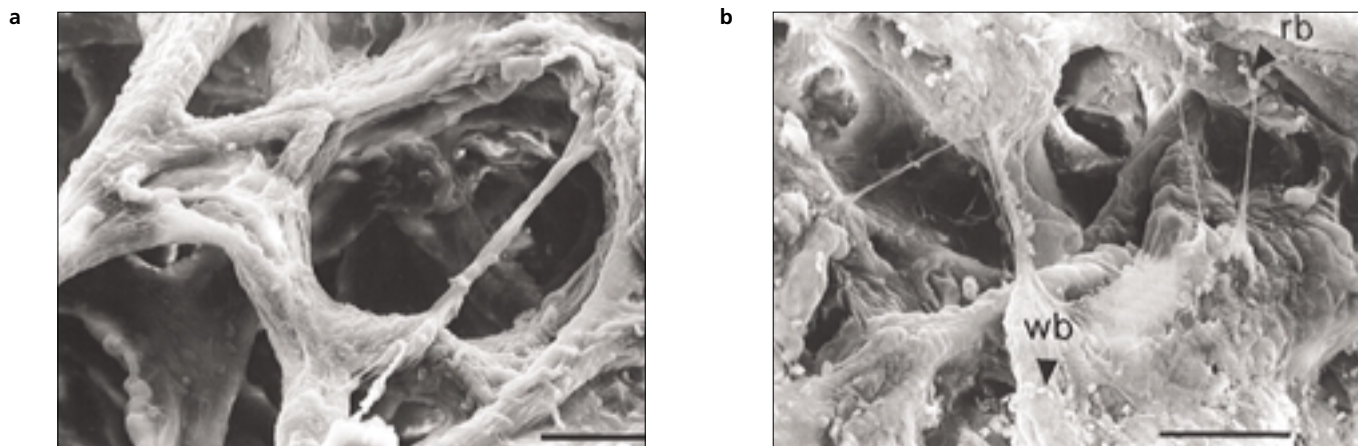


Table 5. Commonly used therapeutic drugs and their effects upon sexual function

Type of drug	Drug/class of drug	Effect
Major tranquillisers	Thioridazine	- Ejaculatory dysfunction
	Phenothiazines	- ED, loss of libido, ejaculatory dysfunction and priapism
	Butyrophenones	- ED and painful ejaculation
Antidepressants	Selective serotonin reuptake inhibitors	- Ejaculatory dysfunction
	Tricyclic antidepressants	- ED and loss of libido
	Endocrine drugs	
Endocrine drugs	Steroidal antiandrogens e.g. cyproterone	- ED and loss of libido
	LHRH analogues	- ED and loss of libido
	Oestrogens	- ED and loss of libido
Antihypertensives	Diuretics	- ED
	β -adrenoceptor blockers	- ED
	Centrally acting agents e.g. α -methyl DOPA	- ED, loss of libido, ejaculatory dysfunction
	α -blockers	- Retrograde ejaculation and priapism
	Others	
Others	Cimetidine	- ED and loss of libido
	Digoxin	- ED
	Metoclopramide	- ED and loss of libido
	Phenytoin, carbamazepine	- ED and loss of libido

thetic nerves that subserve penile erection run adjacent to the prostate and are often damaged during such radical surgery. Techniques of surgery (in particular radical prostatectomy) have been devised with the aim of both nerve and potency preservation.⁸

Other surgery that can lead to ED includes spinal surgery and surgery for Peyronie's disease or for priapism, while radiotherapy

Table 6. The sexual effects of recreational drugs

Alcohol	- ED, arousal disorders, ejaculatory and orgasmic dysfunction
Marijuana	- ED
Amphetamine	- Loss of libido and ejaculatory dysfunction
Opiates	- ED and loss of libido
Cocaine	- ED
Anabolic steroids	- ED and loss of libido

for bladder, prostate or rectal cancer will often lead to delayed ED via a vasculogenic mechanism.

Conclusion

The pathophysiological mechanisms involved in the development of erectile dysfunction are many and varied. A number of mechanisms may be active in an individual, and nowhere is this more true than in men with diabetes. Around 50% of diabetic men can expect to develop ED, and pathophysiological mechanisms involved include peripheral autonomic neuropathy, large vessel atheroma, small vessel microangiopathy, endothelial dysfunction and psychological disorders.⁹

In the general population, the commonest causes of ED are vascular, and there is increasing evidence that the risk factors for atherosclerosis, namely hypertension, smoking, hyperlipidaemia and diabetes, are all strongly associated with ED. This has two important consequences. Firstly, control of these risk factors might be expected to reduce the risk of ED. Second, when men do present with ED, it is important to identify these risk factors, not only to potentially improve the ED, but also to try to prevent other future cardiovascular sequelae.



Key messages

- The pathophysiological mechanisms involved in ED are many and varied
- Around 50% of diabetic men can expect to develop ED
- Diabetic ED is related to peripheral autonomic neuropathy, large vessel atheroma, small vessel angiopathy, endothelial dysfunction and psychological causes.
- Control of risk factors (e.g. hypertension, hyperlipidaemia, diabetes and smoking) will reduce the risk of ED and prevent cardiovascular complications

In conclusion, ED may develop in a number of different ways. Increasing knowledge of these mechanisms will improve our ability to treat men with ED and may also allow us, in the future, to prevent it from arising in the first place.

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