

Male sexual dysfunction



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The main sexual dysfunctions

- Erectile  dysfunction -
- Disorders of ejaculation and orgasm
- Peyronie's disease
- Priapism



ERECTILE DYSFUNCTION

Magic can't solve all your problems.

Erectile Dysfunction

Definition

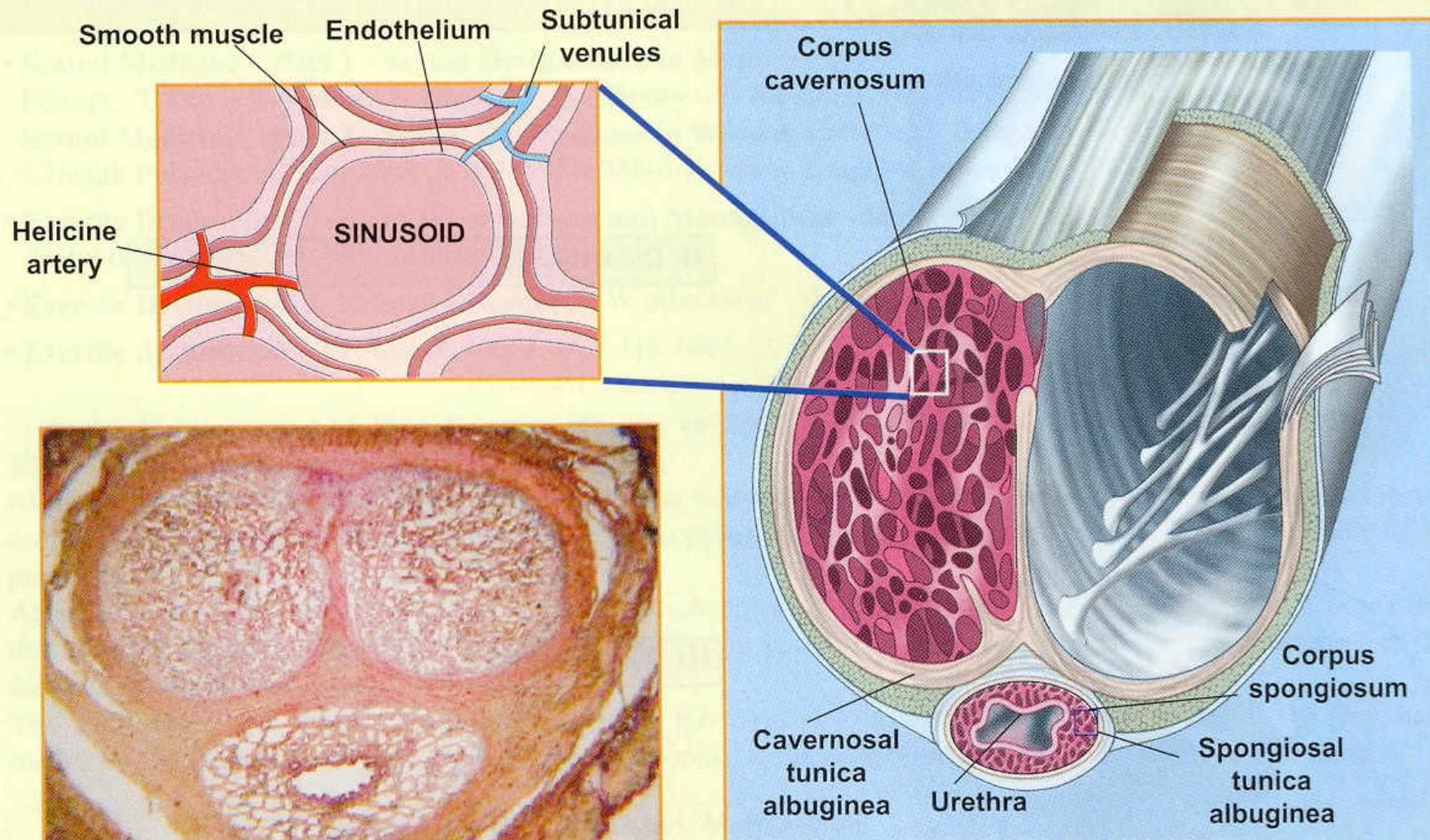


- Erectile dysfunction (ED) is defined as the **persistent** inability to **achieve and/or maintain an erection** sufficient for satisfactory sexual activity.^{1,2}
- “Erectile dysfunction” more precisely defines the nature of this sexual dysfunction than does “impotence.”¹

1. NIH Consensus Development Panel on Impotence. *JAMA*. 1993;270(1):83-90.
2. Montague DK, et al. *J Urol*. 1996;156:2007-2011.

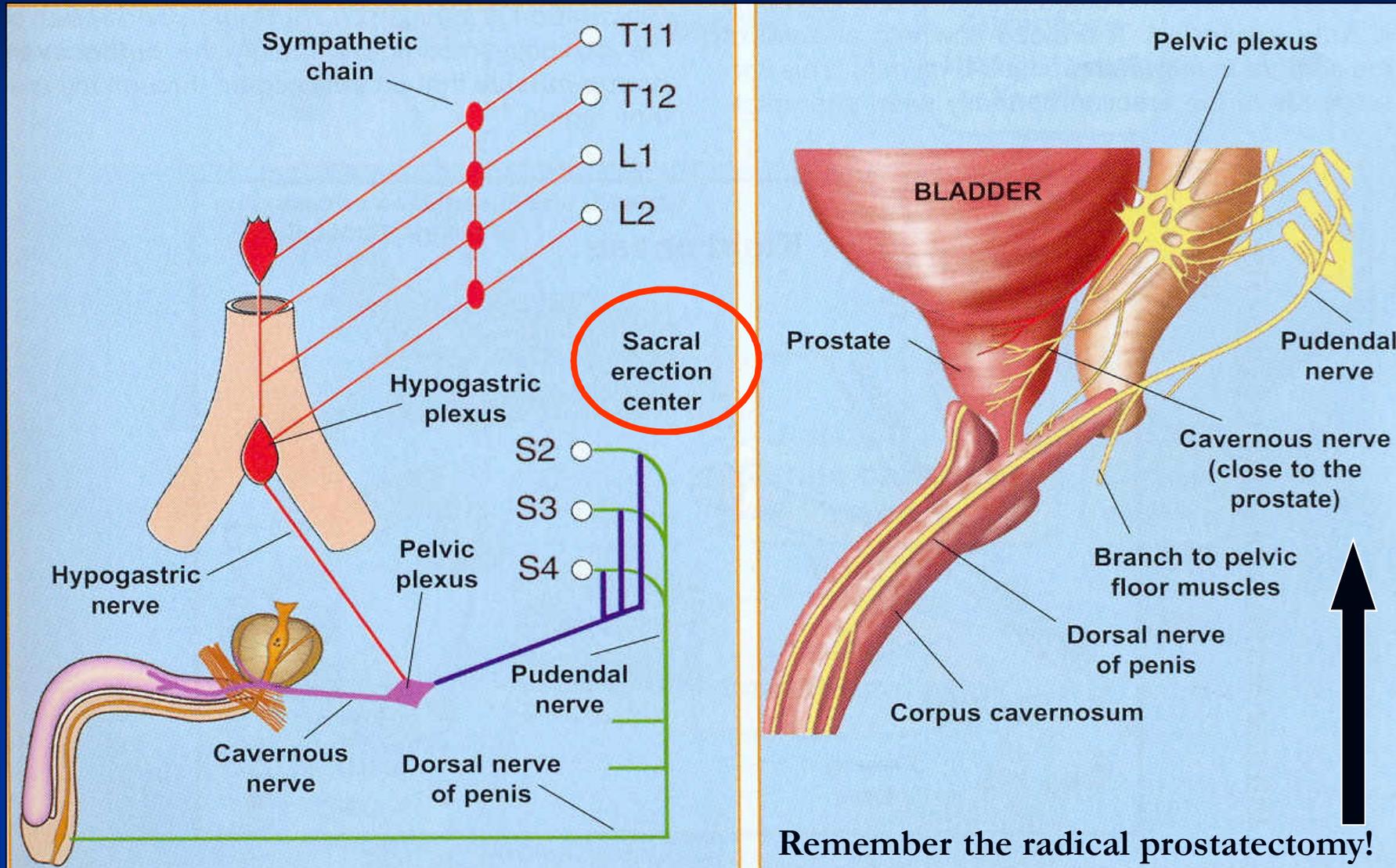
2

The erectile tissue consists of a lattice of vascular sinusoids surrounded by trabecular smooth muscle



C.Cavernosa contain numerous interconnecting vascular spaces – **SINUSOIDS** – within a fibromuscular framework.

Innervation of the Penis



Sexual Cycle in Man

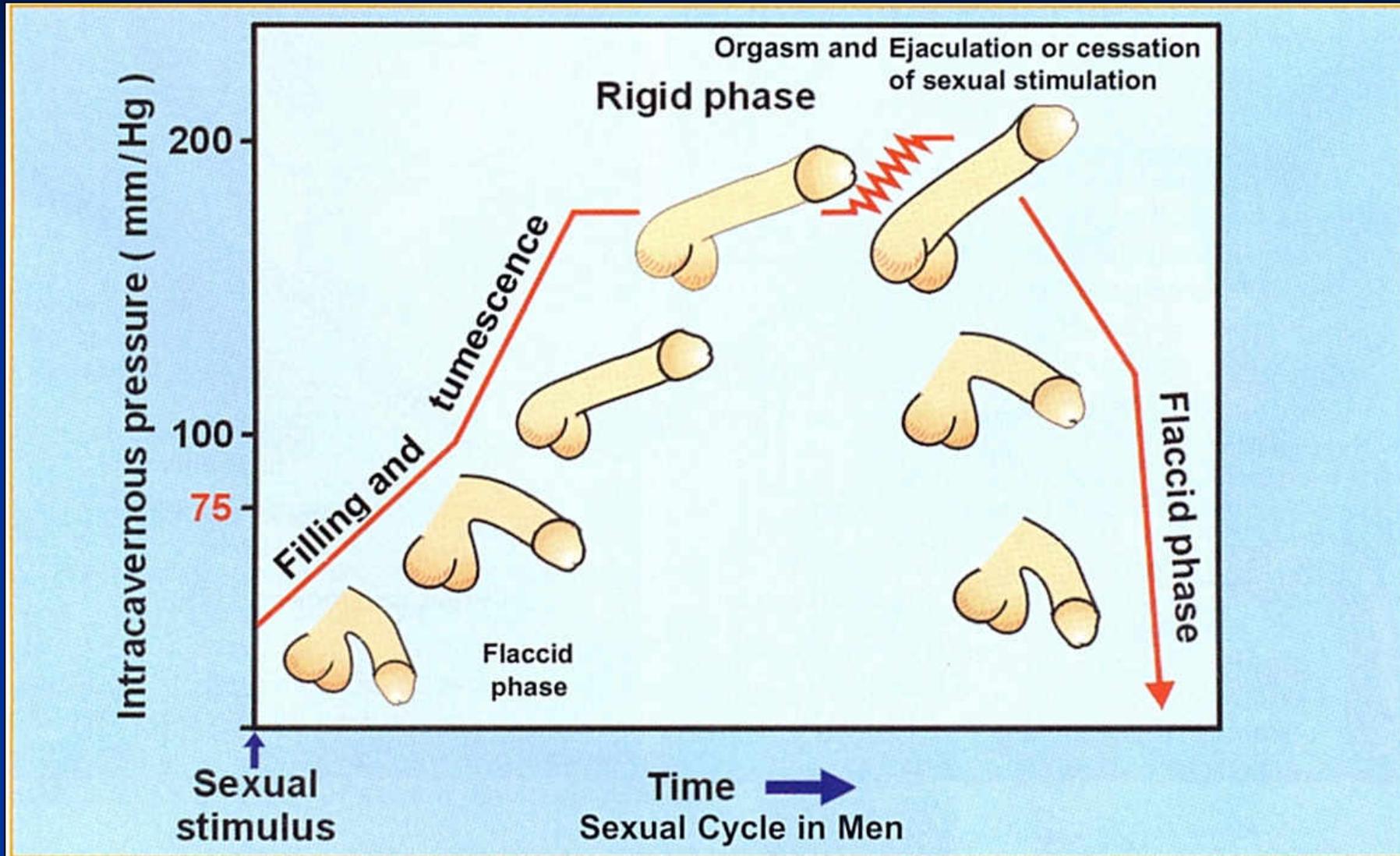
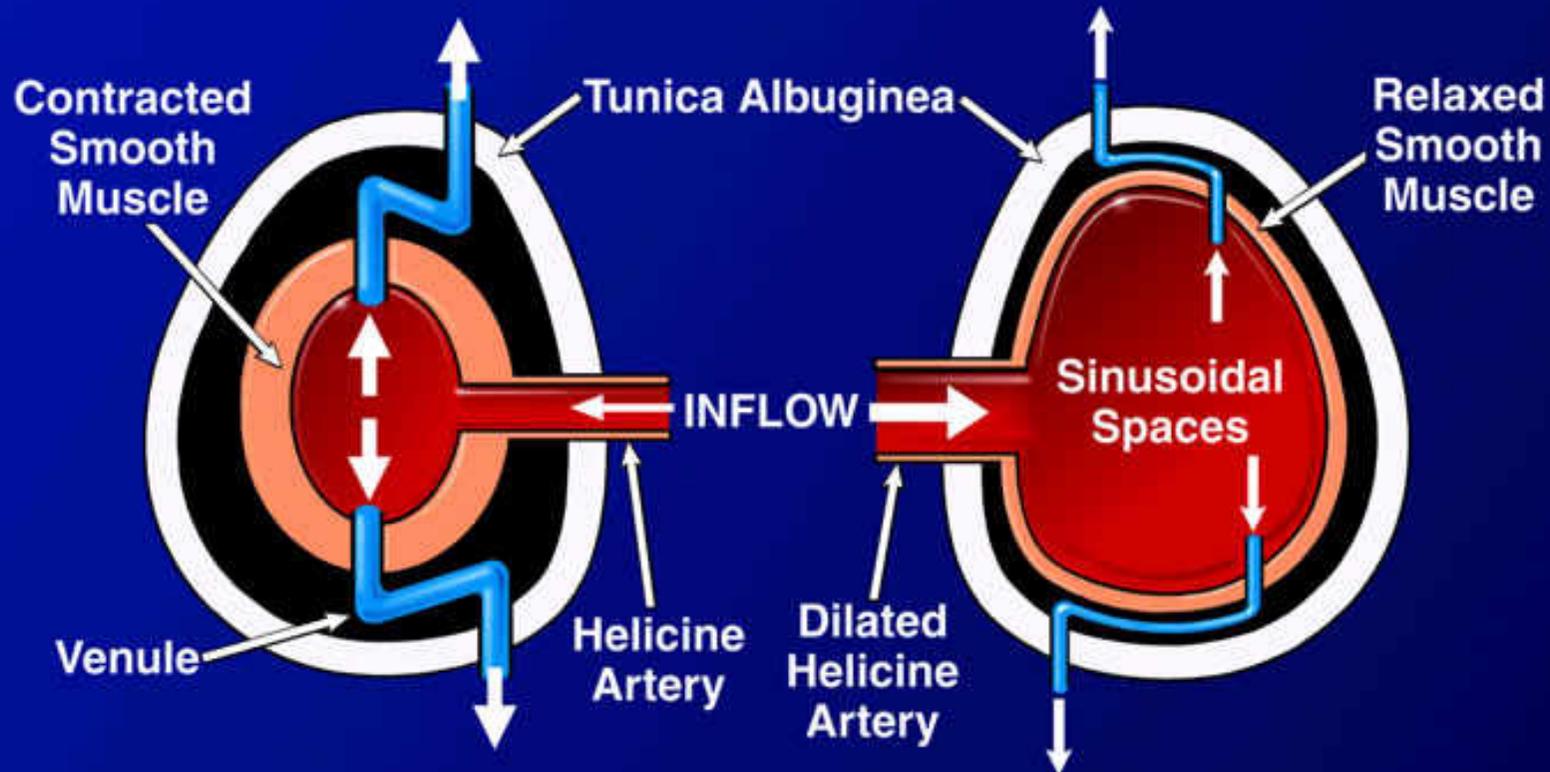




Diagram of penile erection



Sympathetic predomination

FLACCID

RIGID

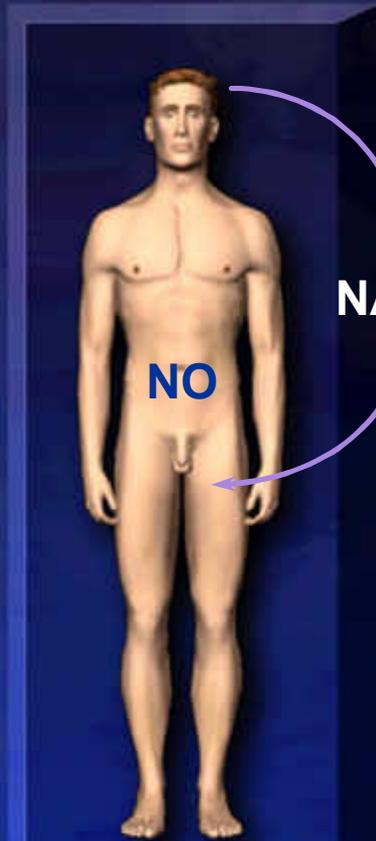
Parasympathetic predomination

The main components: increase of arterial inflow ↑
smooth muscle relaxation ↓
restriction of venous outflow ↓

The „chemistry” of erection



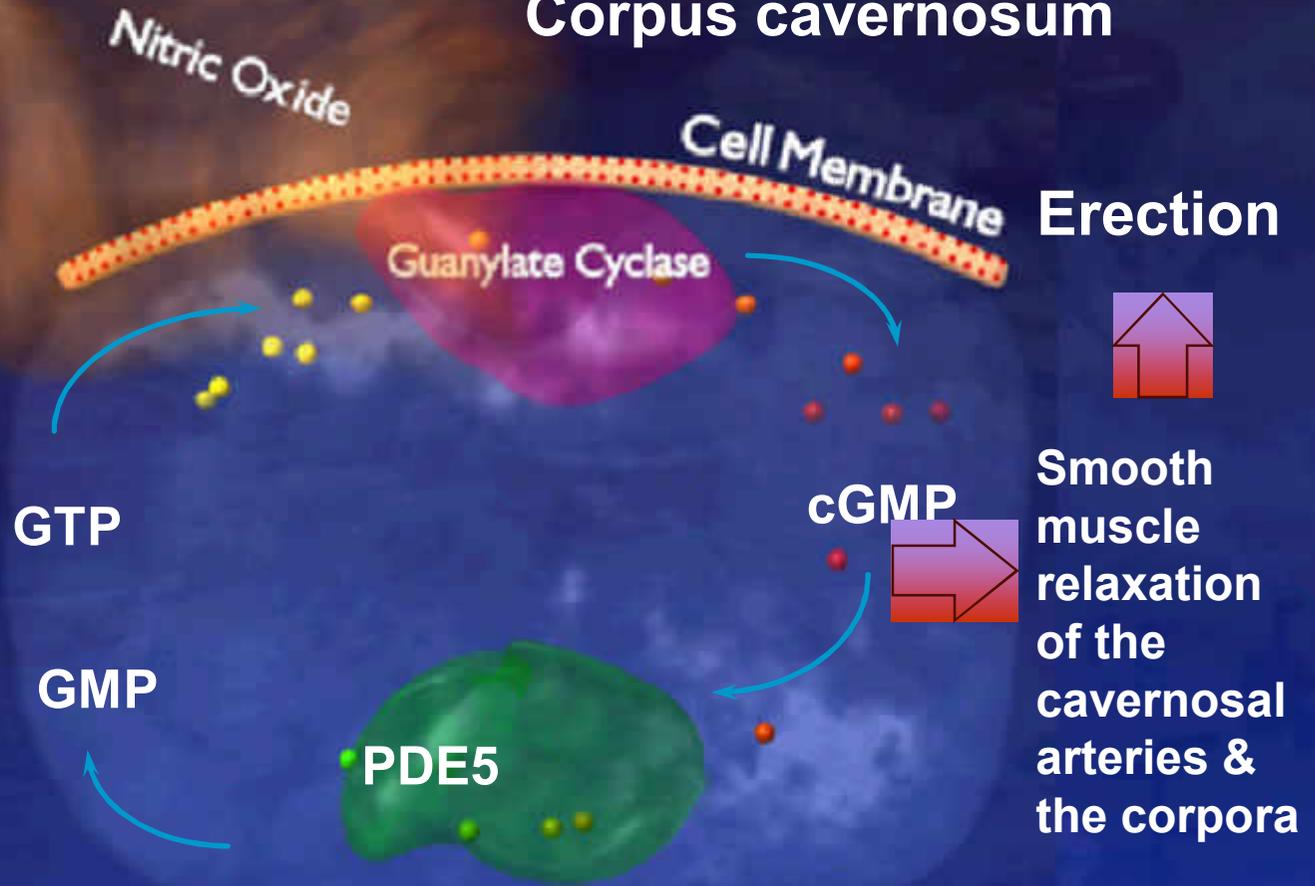
Sexual stimulation



NANC

NO

Corpus cavernosum



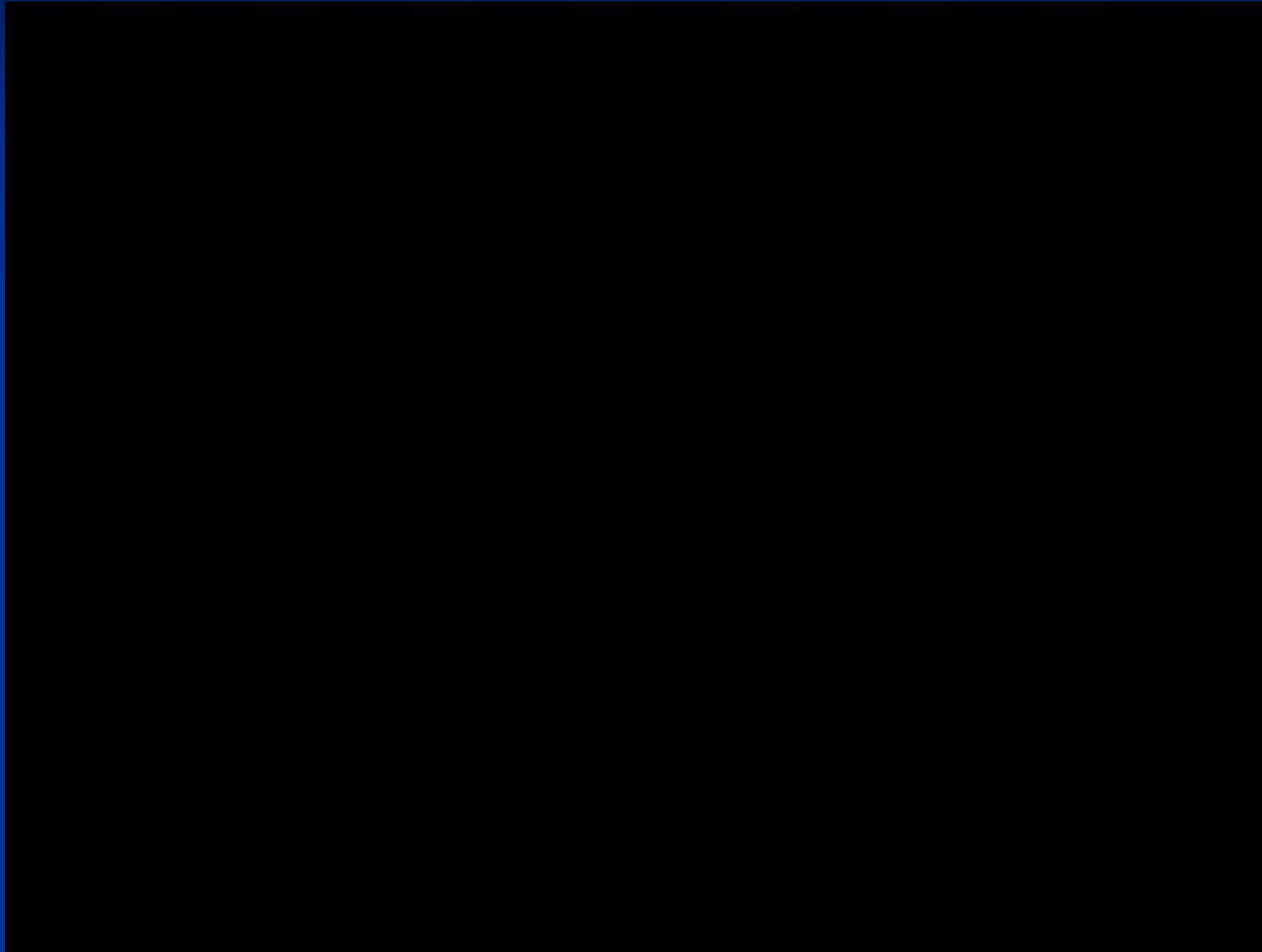
Erection



Smooth muscle relaxation of the cavernosal arteries & the corpora

NO=nitric oxide; NANC=nonadrenergic-noncholinergic neurons; PDE5=phosphodiesterase type 5

The „physics” of Erection



The „chemistry” of Erection

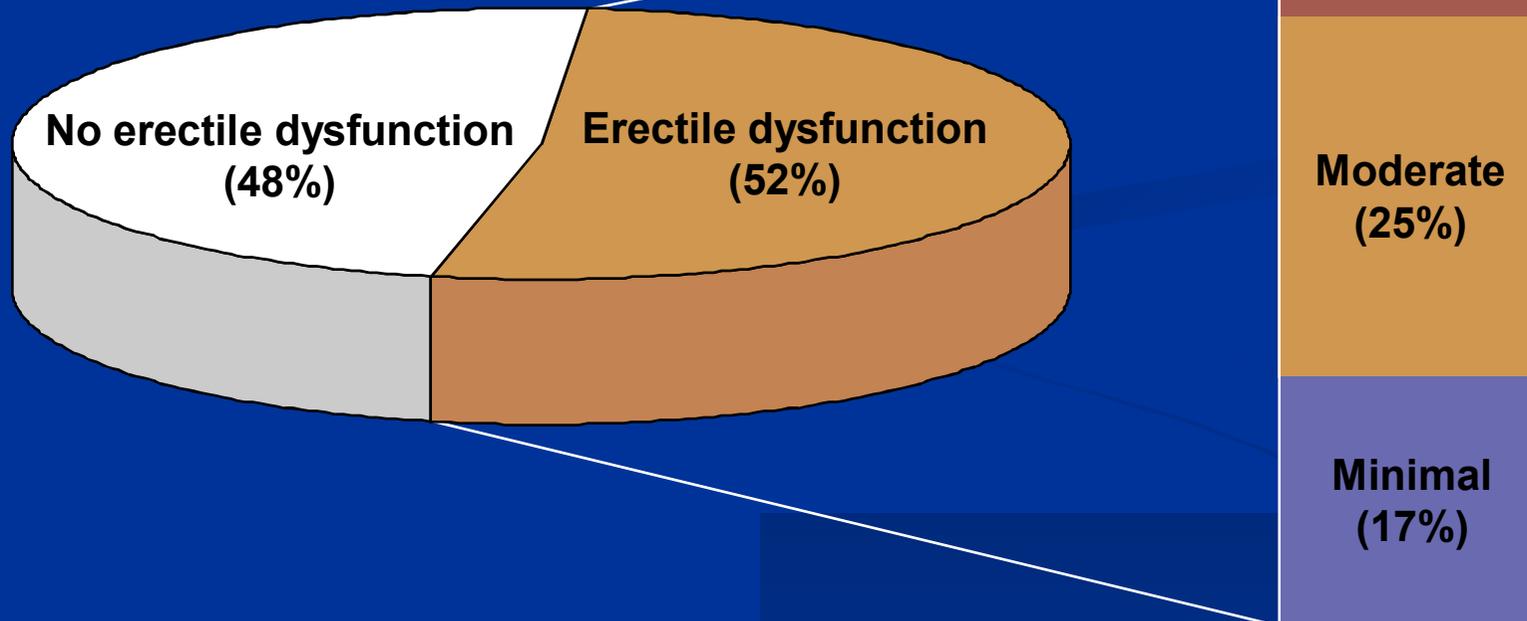


Erectile Dysfunction

Prevalence & Severity

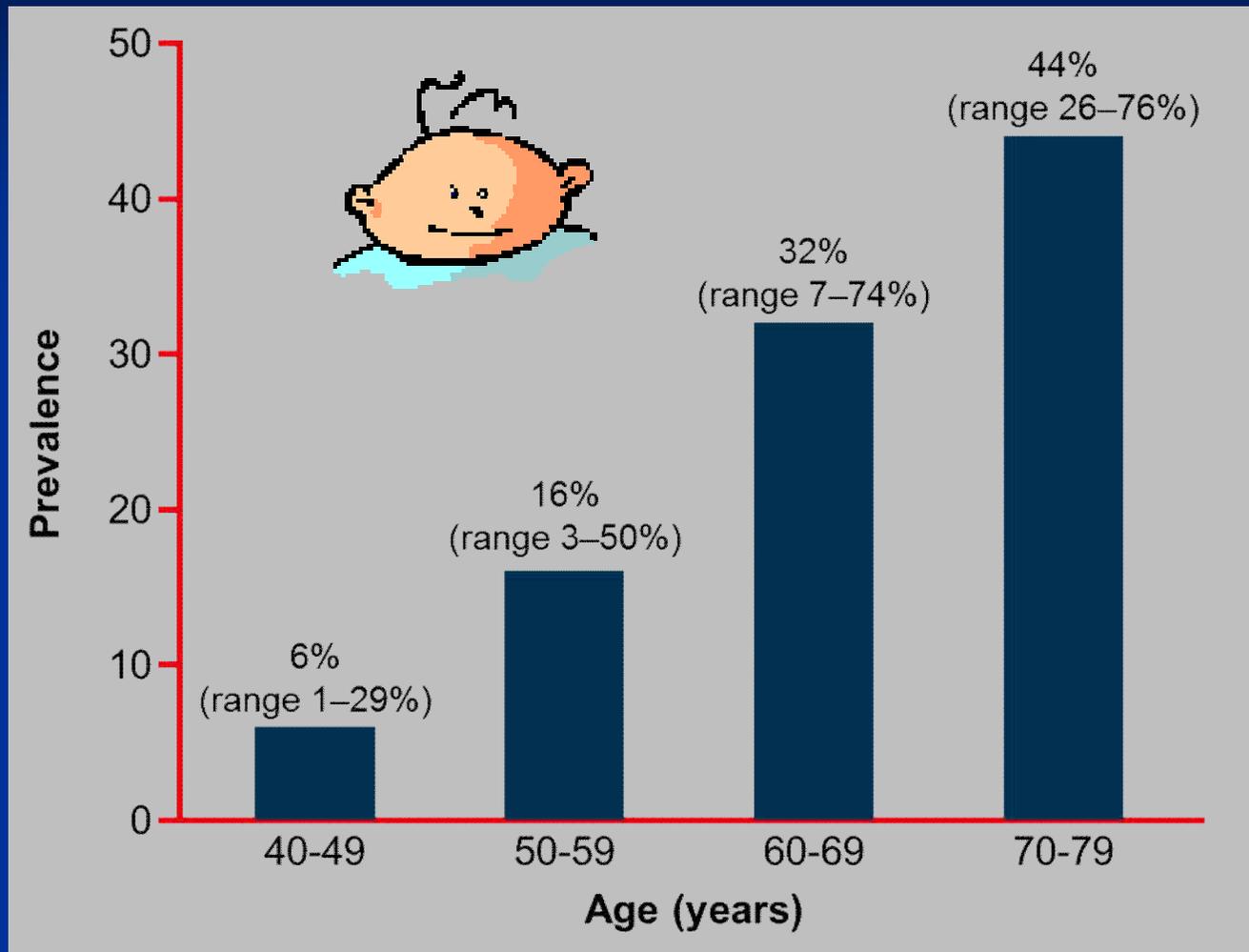
Massachusetts Male Aging Study¹

Men aged 40 to 70
years



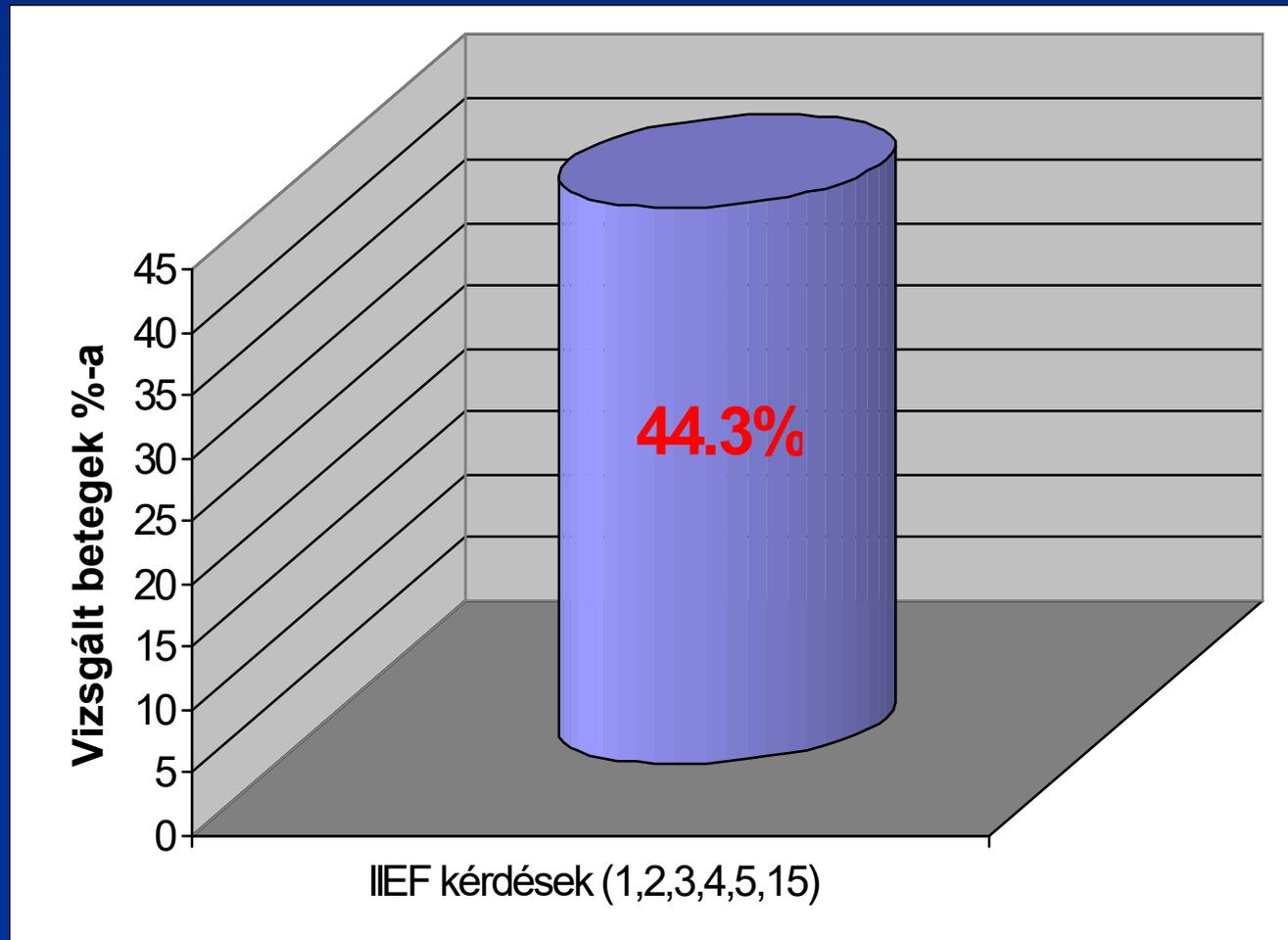
Feldman HA, et al. *J Urol.* **1994**;151:54-61.

ED prevalence

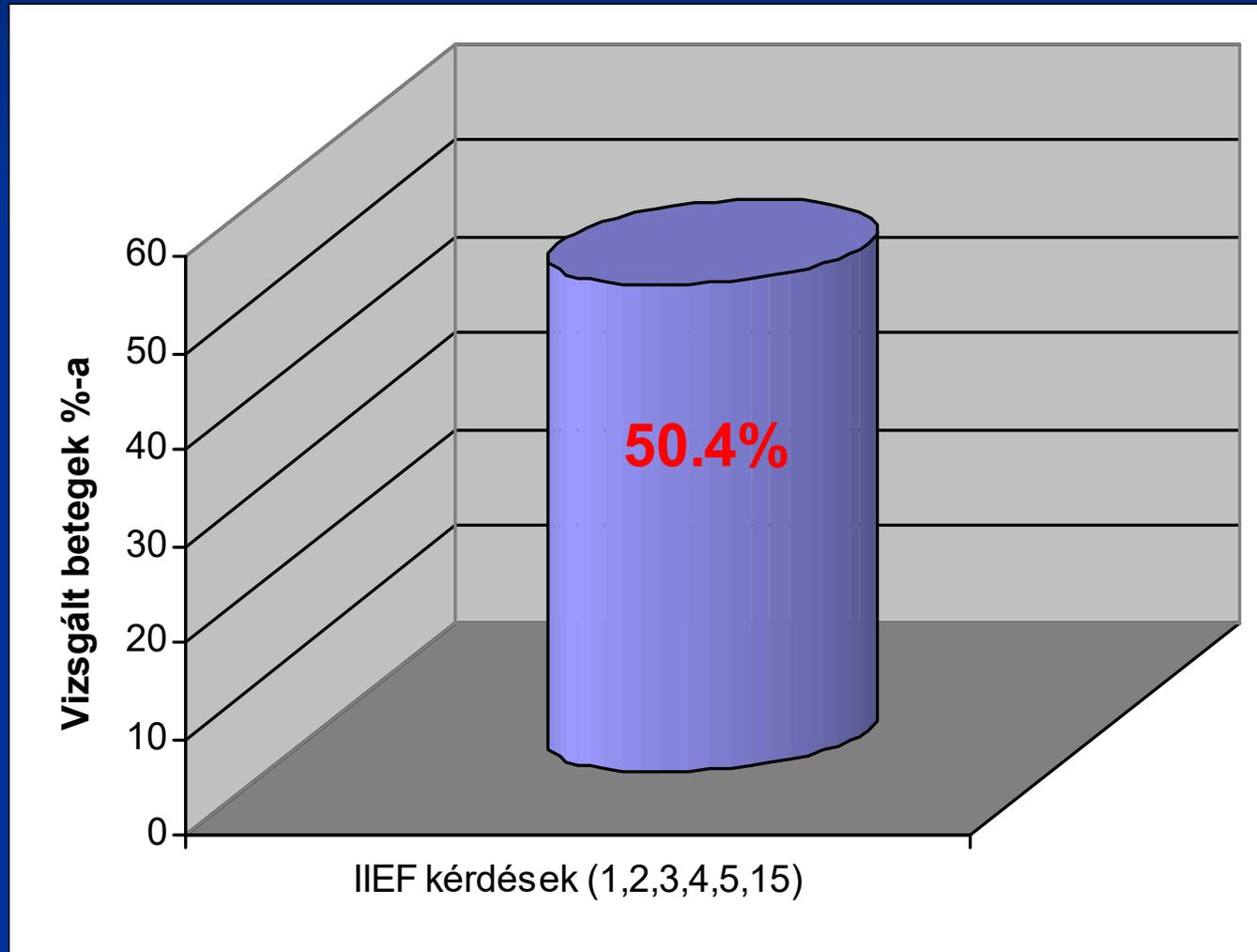


Data from 34 studies

The prevalence of ED between the Hungarian **Hypertonia** Patients



The prevalence of ED between the Hungarian **Urological** Patients



4. Data on file, Pfizer

Budapest

Erectile Dysfunction

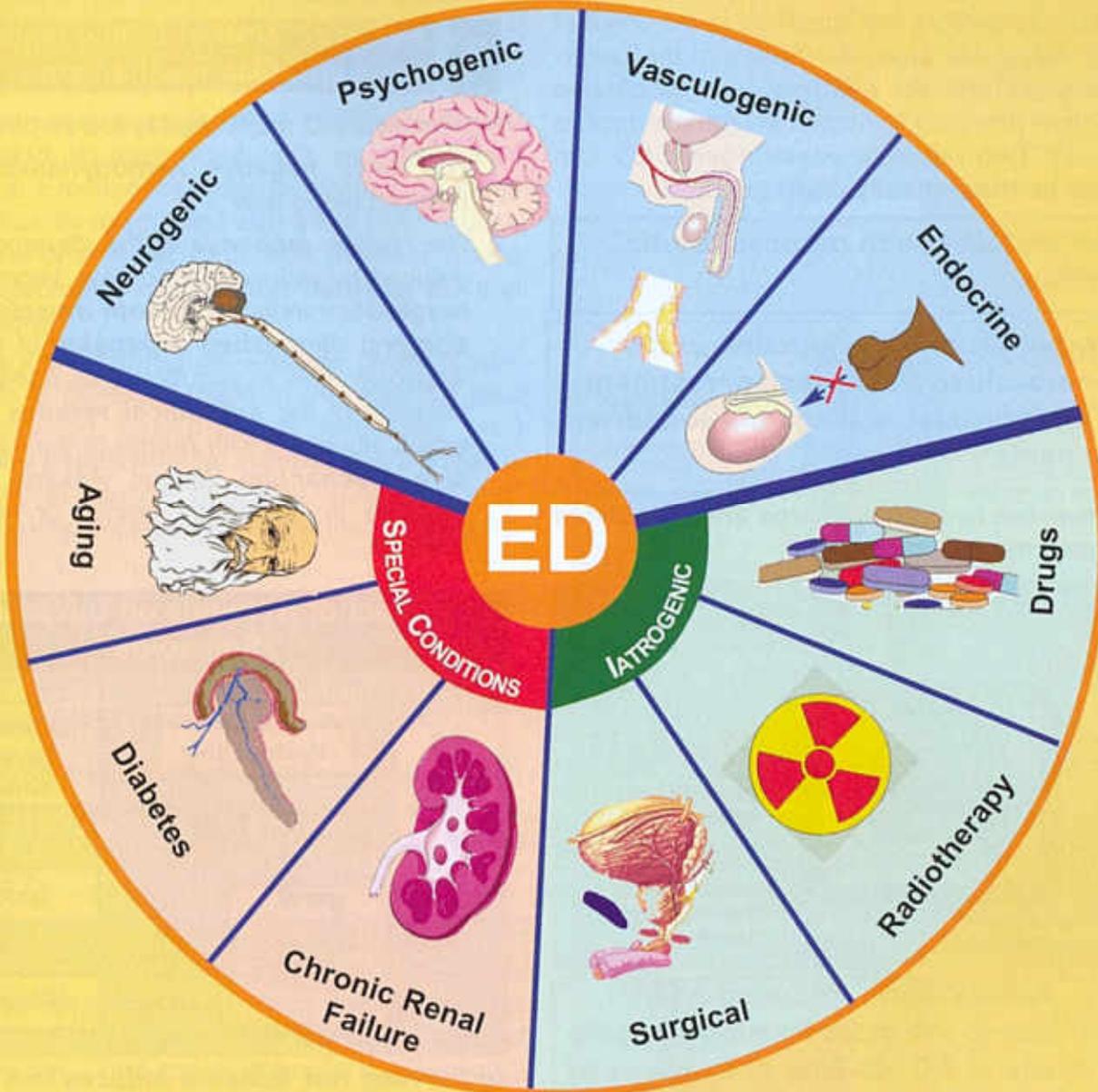
Etiology

ED can be classified as

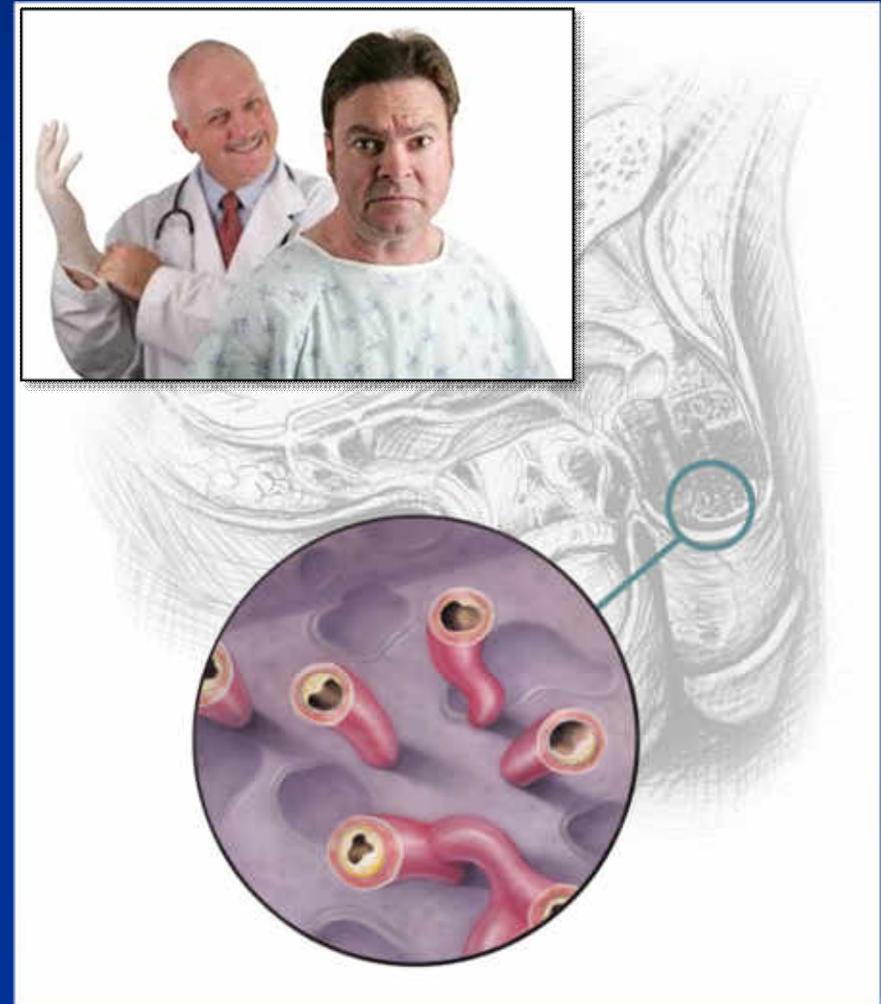
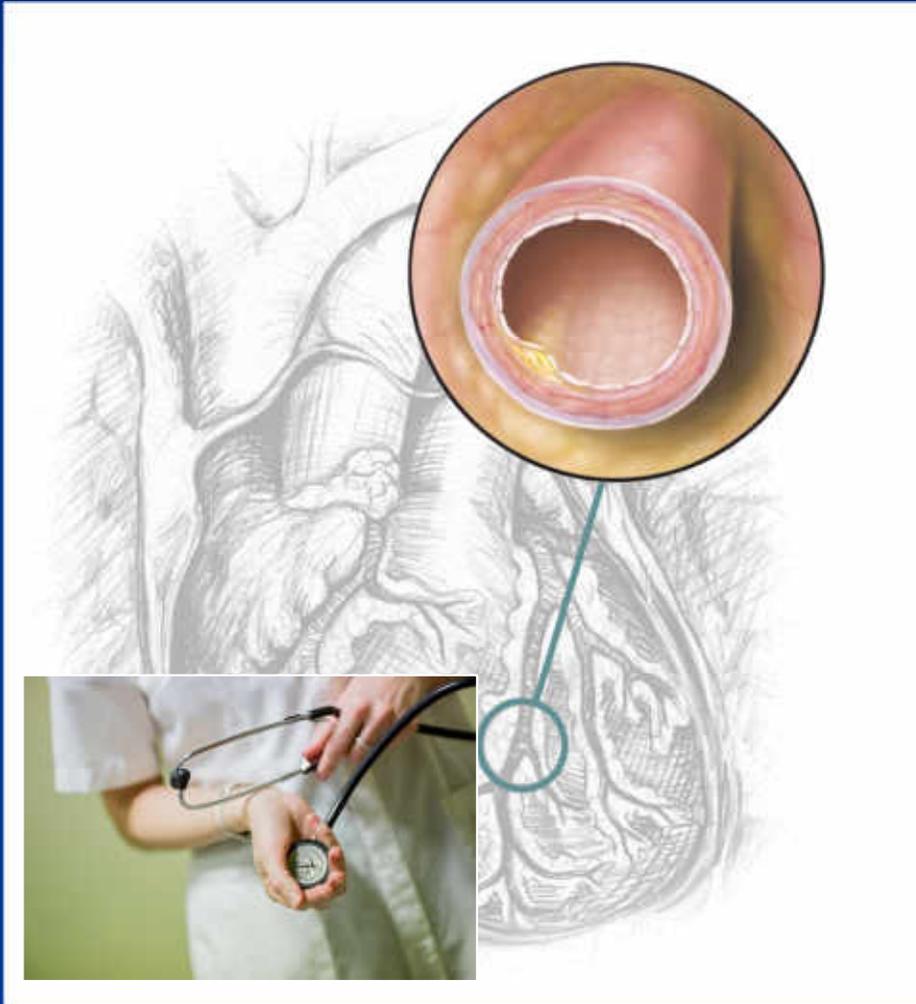
- organic: due to **vasculogenic**, neurologic, hormonal, or cavernosal abnormalities or lesions
- psychogenic: due to central inhibition of the erectile mechanism without a physical insult
- mixed organic/psychogenic: due to a combination of organic and psychogenic factors.

1. NIH Consensus Development Panel on Impotence. *JAMA*. 1993;270(1):83-90.
2. Benet AE, et al. *Urol Clin North Am*. 1995;22(4):699-709.

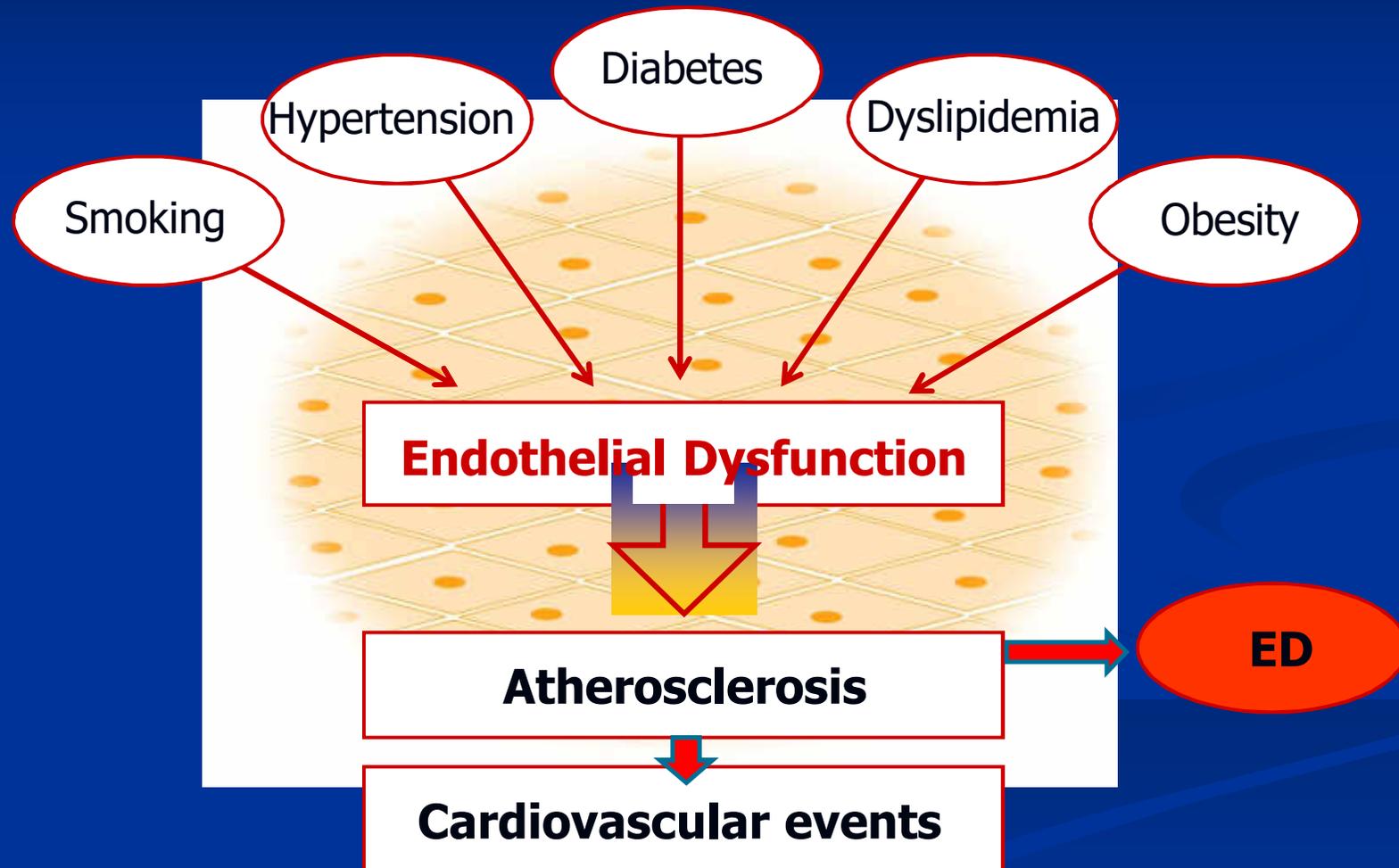
PATHOPHYSIOLOGY



The two „ED-s”

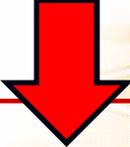


Endothelial Dysfunction as a **Precursor** of Vascular Events



Definition of Endothelial Dysfunction

Presence of several or all of the following pathomechanisms:

- 
- **Impaired NO-Synthesis and inactivation of NO** 
 - **Reduced ability of vasodilatation** 
 - **Increased thrombocyte aggregation**
 - **Increased leukocyte adhesion**
 - **Increased proliferation of endothelial smooth muscle**
 - **Decreased number of endothelial progenitor cells (EPCs)**

Risk factors

CVD

- Age
- Gender
- Hypertonia
- Diabetes
- Hyperlipidaemia
- Obesity
- Smoking
- Lifestyle

ED

- Age
- Diabetes
- Hypertonia
- Hyperlipidaemia
- Urological illnesses
- Smoking-alcohol
- Side effects (Drugs)
- CVD

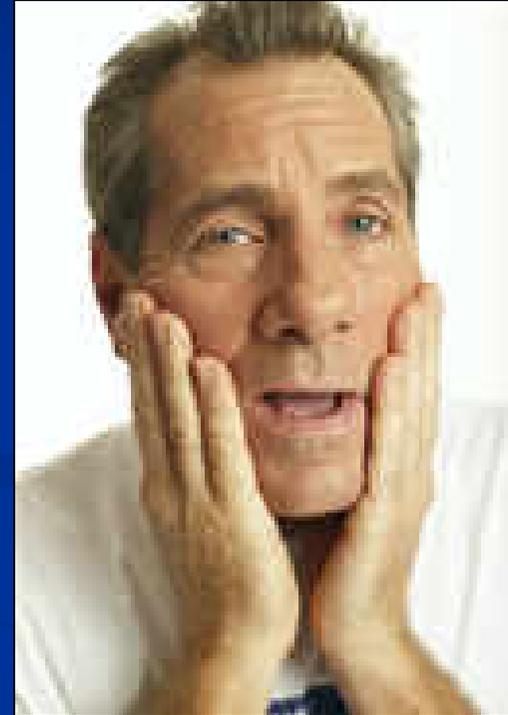
What students need to know about **ED** and **CVD**

- ED and CVD share **common risk factors**
- CVD is a risk factor for ED
 - **ED and CVD develop in response to impaired endothelium-dependent vasodilation**

Feldman HA et al. J Urol 1994; 151: 54–61
Zusman RM. Am J Cardiol 1999; 83 (5A): 1C–2C

Why is it **important to identify** men with ED ?

- ED can be associated with a lot of psychosexual morbidity
 - anxiety and depression
 - decreased self-esteem
 - negative effect on relationships
- ED screenings may also **uncover underlying diseases** 
 - diabetes
 - hypertension
 - dyslipidemia and CVD
 - certain malignancies
- Identifying ED can reveal medication and compliance issues



Goldstein I et al. N Engl J Med 1998; 338: 1397–1404

Shabsigh R et al. Urology 1998; 52: 848–852

NIH Consensus Development Panel. JAMA 1993; 270: 83–90

ED as an Early Marker of CVD!

162 angiographically assessed men with symptomatic CVD
(mean age 54-56 years)

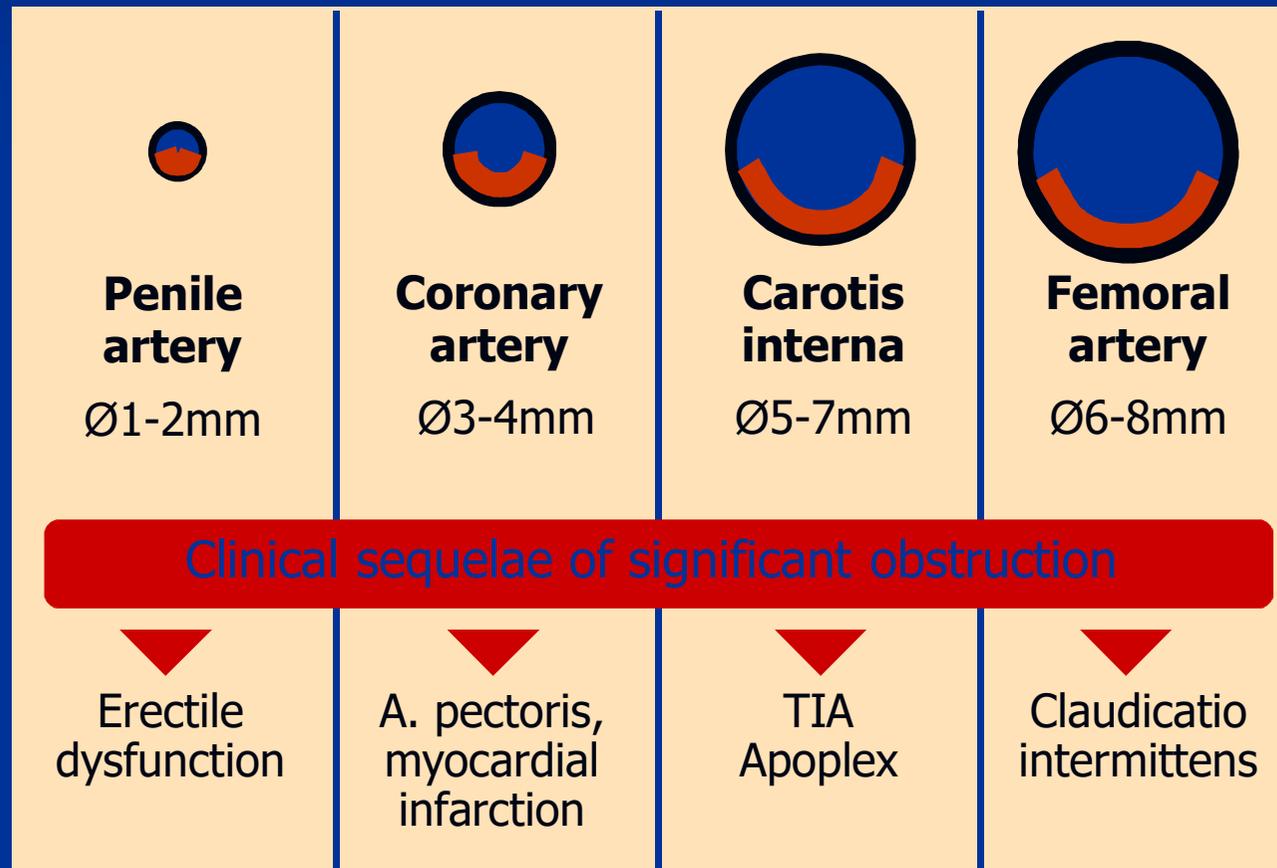
CVD-severity	n	ED-Prevalence	
1 stenotic artery	56	18%	} mean prevalence 46%
2-3 stenotic arteries	53	57%	
Chronic angina	53	66%	

**In 71% of patients with chronic angina
ED preceded CVD
(mean interval 25 months) !!!**



Why does ED Occur before Cardiovascular Diseases?

Hypothesis: Arterial diameter



Don't forget !

Erectile

Dysfunction

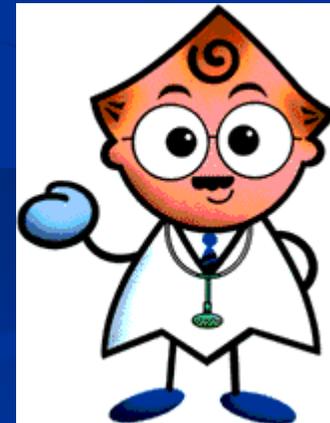
ED

Endothel

Dysfunction

(lipids, glucose, BP)

Early **D**etection



I. BASIC EVALUATION

1

Medical, Psychosocial and Sexual Assessment
Questionnaire



2

Physical Examination



3

Laboratory Tests

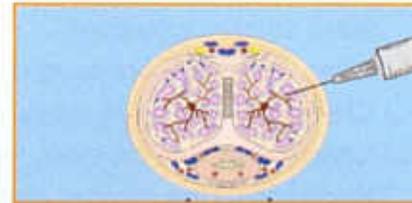
(testosterone, PSA, lipid profile, blood sugar...)



II. SELECTED OPTIONAL TESTS

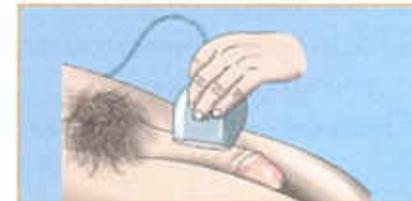
1

Pharmacological Testing



2

Color Doppler Imaging (CDI)



International Index of Erectile Function (IIEF)



- Brief, reliable, multidimensional 15-item questionnaire
- Significant sensitivity, specificity, reliability and discriminant power¹
- Linguistically **validated** in more than 30 languages

International Index of Erectile Function

Erectile Function Domain	0	1	2	3	4	5
How often were you able to get an erection during sexual activity?		X				
When you had erections after stimulation, how often were your erections hard enough for penetration?		X				
When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?				X		
During sexual intercourse, how often were you able to maintain erection after you had penetrated (entered) your partner?						
During sexual intercourse, how difficult is it to maintain your erection to completion of intercourse?			X			
How do you rate your confidence that you could get and keep an erection?				X		
Total score	11 = moderate EF score					

0 = No sexual activity
 1 = Almost never/never
 2 = A few times (much less than half the time)
 3 = Sometimes (about half the time)
 4 = Most times (much more than half the time)
 5 = Almost always/always

Rosen RC, et al. *Urology*. 1997;49:822-830.

Table 2 – Specific diagnostic tests

- Nocturnal penile tumescence and rigidity (NTPR) using Rigiscan[®]
- Vascular studies
 - Intracavernous vasoactive drug injection
 - Duplex ultrasound of the cavernous arteries
 - Dynamic infusion cavernosometry or cavernosography (DICG)
 - Internal pudendal arteriography
- Neurologic studies (eg, bulbocavernosus reflex latency, nerve conduction studies)
- Endocrinology studies
- Specialized psychodiagnostic evaluation

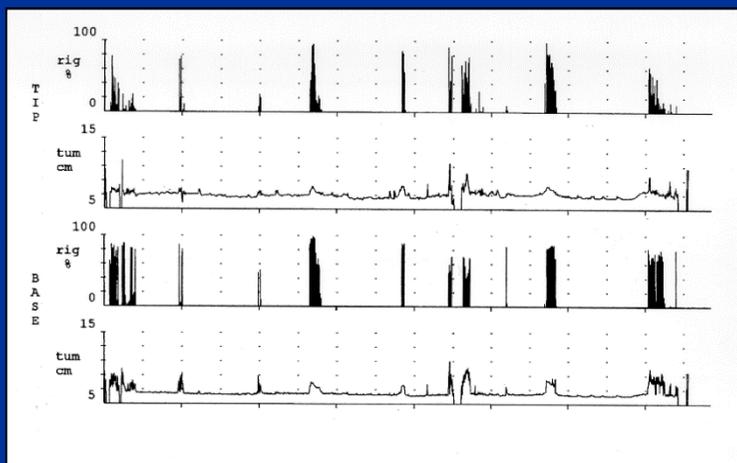


Table 1 – Indications for specific diagnostic tests

- Primary erectile disorder (not caused by organic disease or psychogenic disorder)
- Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery
- Patients with penile deformities (eg, Peyronie disease, congenital curvature) that might require surgical correction
- Patients with complex psychiatric or psychosexual disorders
- Patients with complex endocrine disorders
- Specific tests may be indicated at the request of the patient or his partner
- Medicolegal reasons (eg, implantation of penile prosthesis, cases of sexual abuse)



The Treatment of ED

FIRST LINE THERAPY

PDE5 inhibitors Vacuum devices



SECOND LINE THERAPY

Intracavernosus Intraurethral
Injections alprostadil



THIRD LINE THERAPY

Penile prosthesis implantation

PDE5 inhibitors



cGMP



Caffeine



Sildenafil



Vardenafil



Tadalafil



VIAGRA®

1998



LEVITRA®

2003



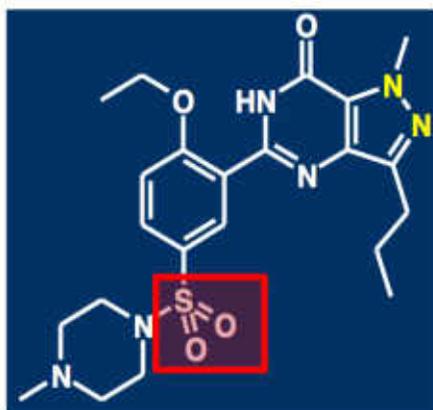
CIALIS®

2003

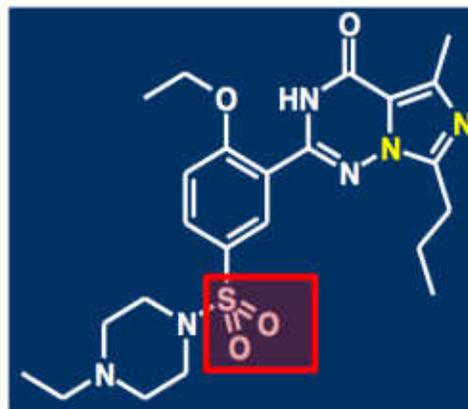
By the way, original production area?

Avanafil: a different molecular structure

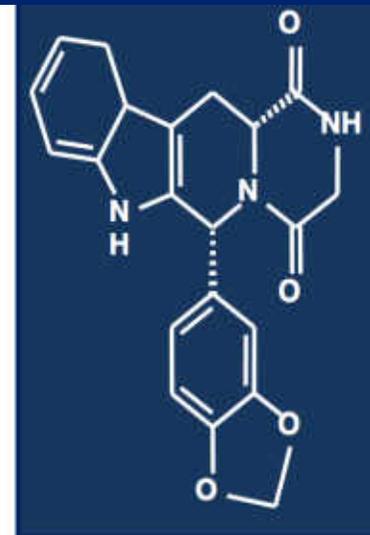
SPEEDRA®



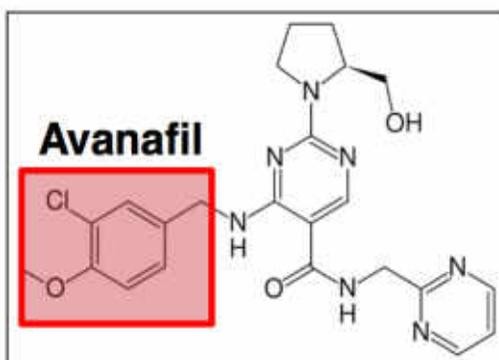
Sildenafil



Vardenafil



Tadalafil



Avanafil

- Highly potent, selective and reversible inhibitor of PDE5
- Unique chemical structure compared with other PDE5 inhibitors
 - Central structure formed by a nitrogen derivative of a pyrimidine carboxamide
 - Sugar component is a cyclic chloromethoxybenzylamino structure
 - Exists as a single enantiomer
 - Binds to catalytic site of PDE5 regardless of spatial orientation,

→ increased affinity for PDE5

The PDE „Family”

PHOSPHODIESTERASES

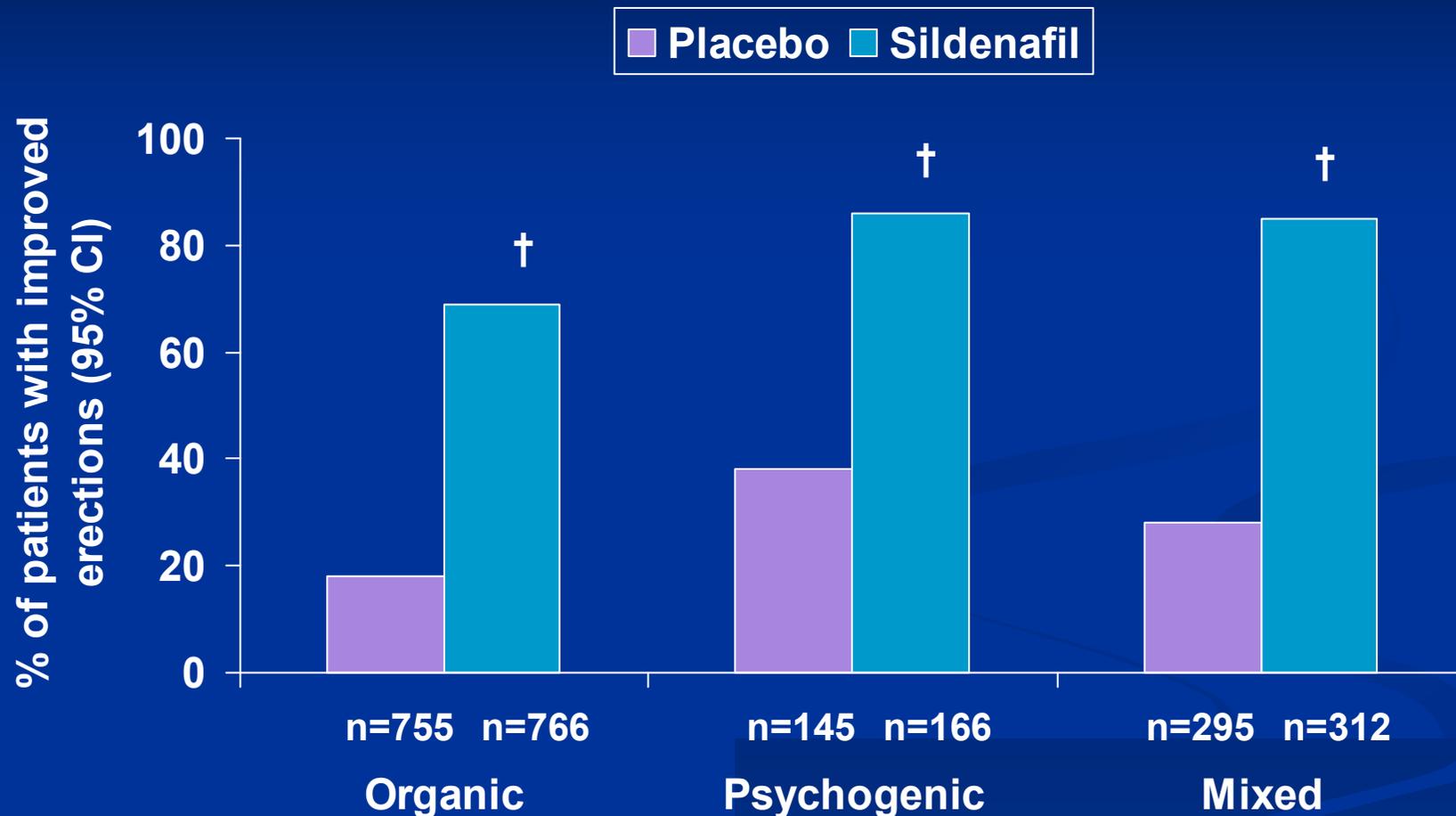
Family	Tissue distribution
PDE1	Brain, lung, heart
PDE2	Brain, adrenal cortex, liver, goblet cells, olfactory neurons
PDE3	Smooth muscle, platelets, cardiac muscle, liver
PDE4	Very wide tissue distribution
PDE5	Smooth muscle (penis++), platelets, kidney
PDE6	Retina
PDE7	Skeletal muscle
PDE8	Testis, ovary, gastrointestinal tract
PDE9	Spleen, gastrointestinal tract, brain
PDE10	Brain, testis, thyroid
PDE11	Smooth muscle, cardiac muscle, testis

The side effects of PDE5 inhibitors are due to : PDE5 is present in **organs other than the penis**



- the drug inhibit **other PDE isoenzymes**

Sildenafil is effective in **all types of ED**

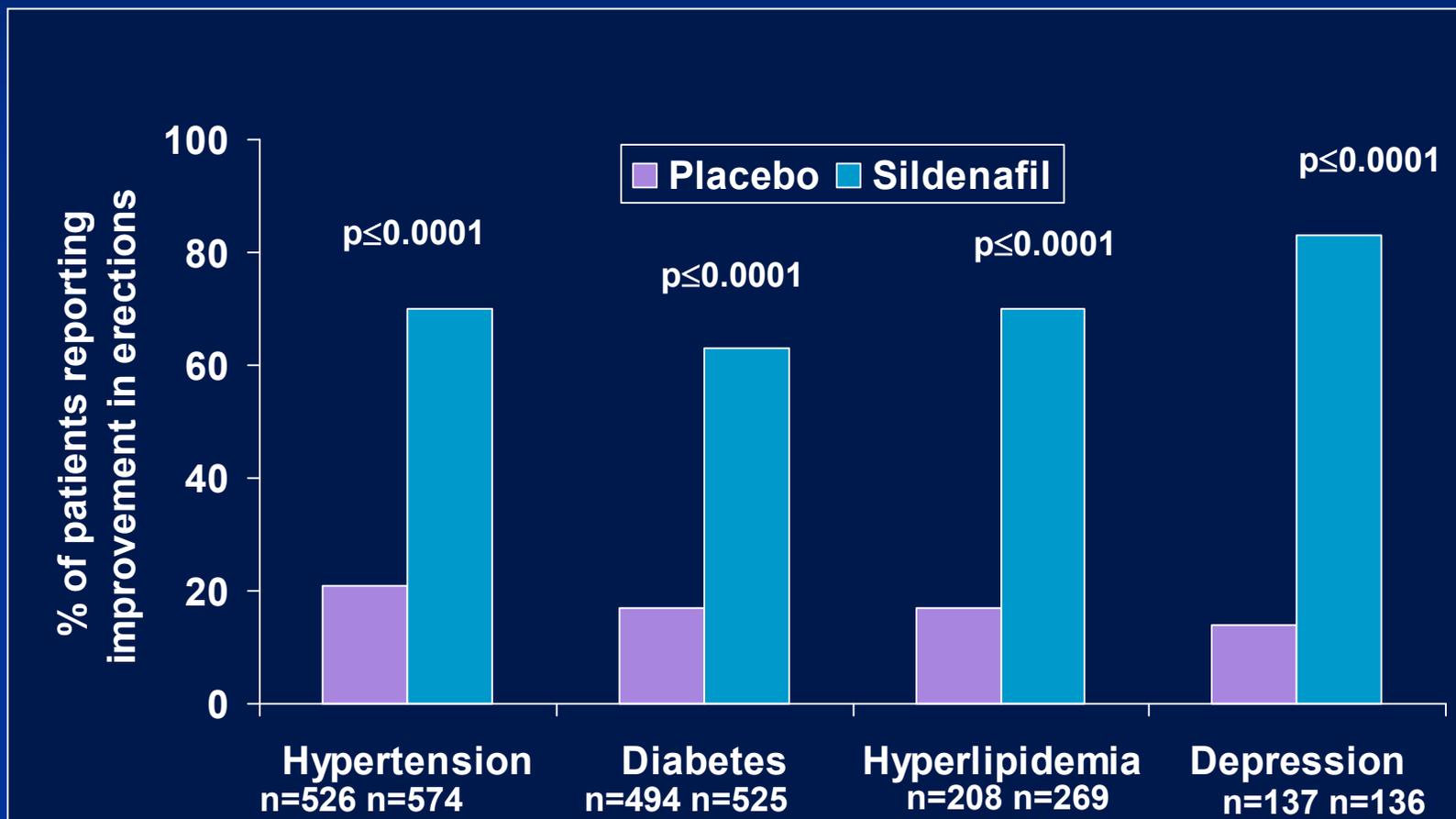


†p=0.0001 sildenafil vs placebo

Data on file. Pfizer Inc, NY

Based on a retrospective analysis of the intent-to-treat population at week 12 from eleven phase III, double-blind, placebo-controlled, flexible-dose studies

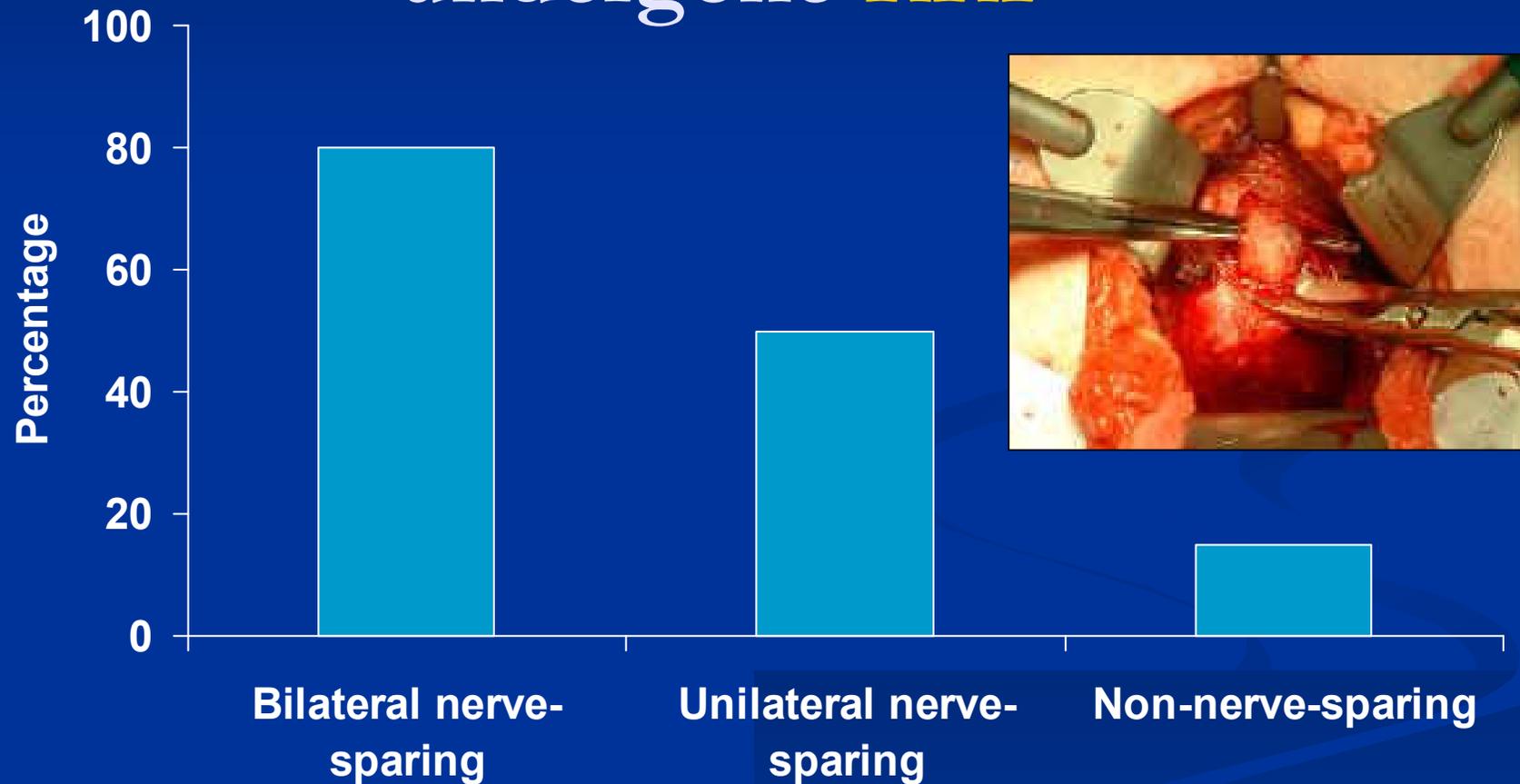
Sildenafil is effective in patients with a variety of medical conditions



In all Phase II, III and IV prn flexible-dose, placebo-controlled studies

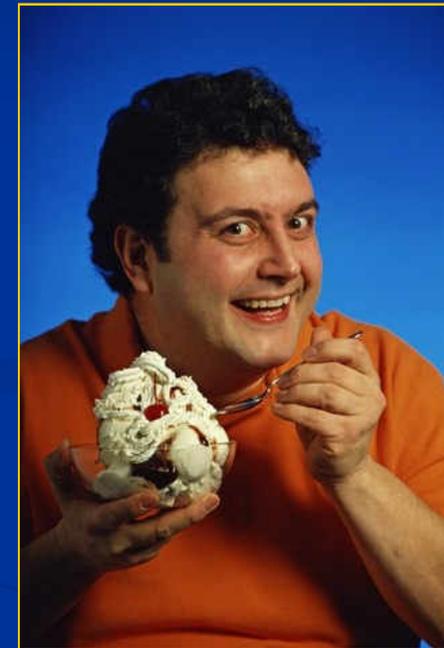
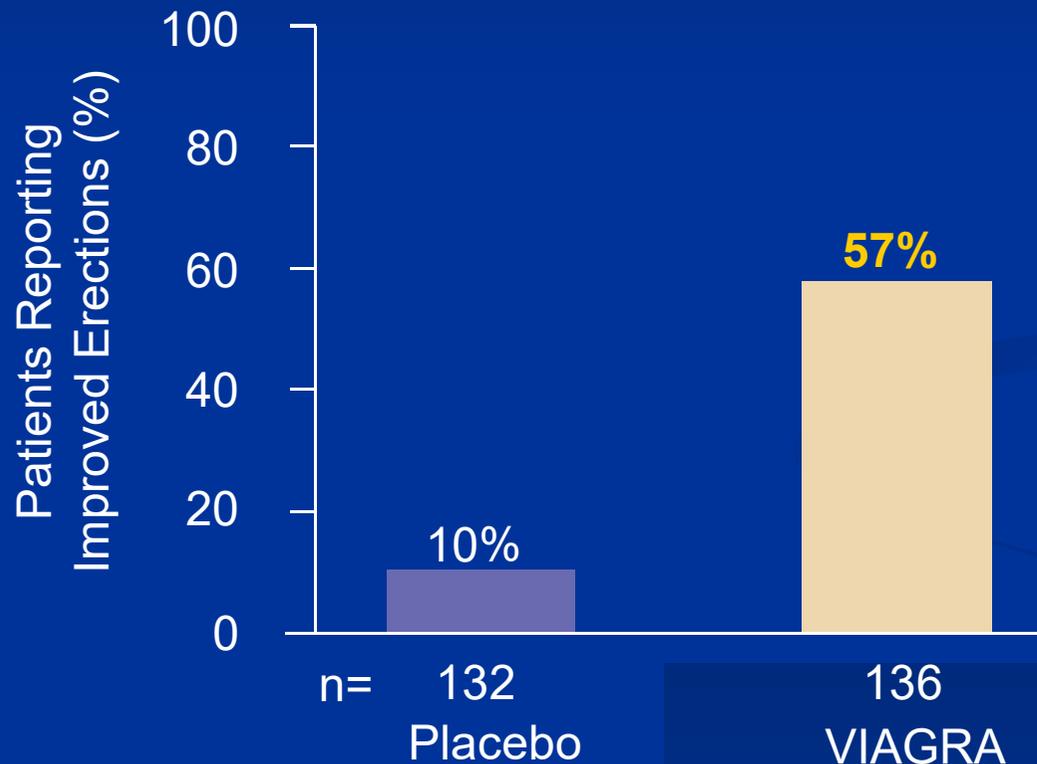
Kloner R, Brown M. Am J Hypertens 2001; 14: 70-73
Data on file. Pfizer Inc, NY

Maximum response rates to sildenafil in men who have undergone **RRP***



Zippe CD et al. Urology 1998; 52: 963–966; Zippe CD et al. Urology 2000; 55: 241–245
Zagaja GP et al. Urology 2000; 56; 631–634

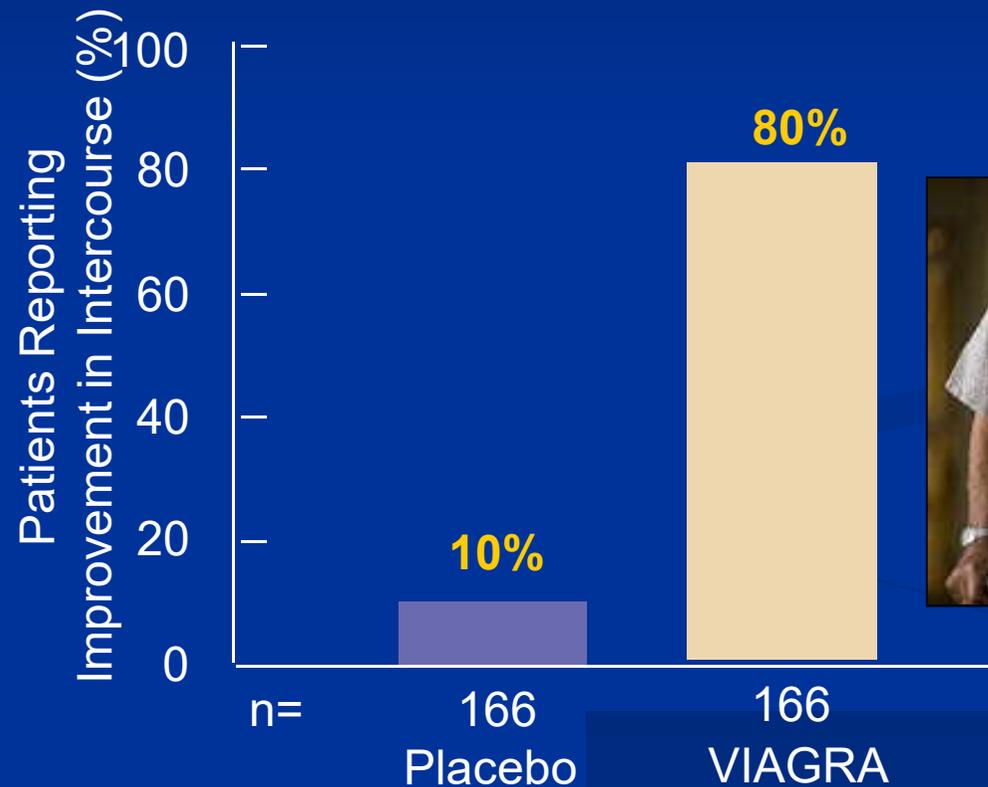
Improvement in Erections in Patients With **Diabetes***



* in 3-Month Flexible-Dose Study

Data on file, Pfizer
Inc.

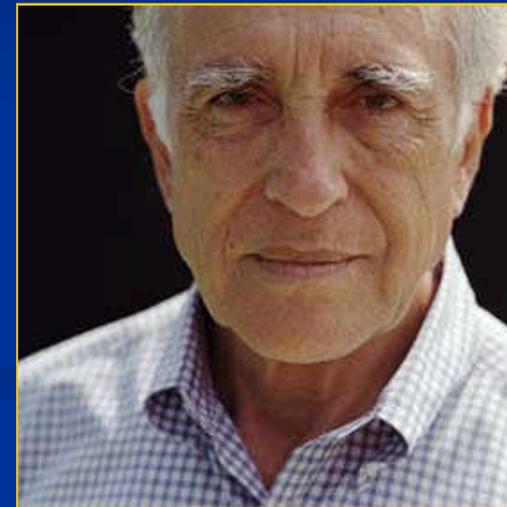
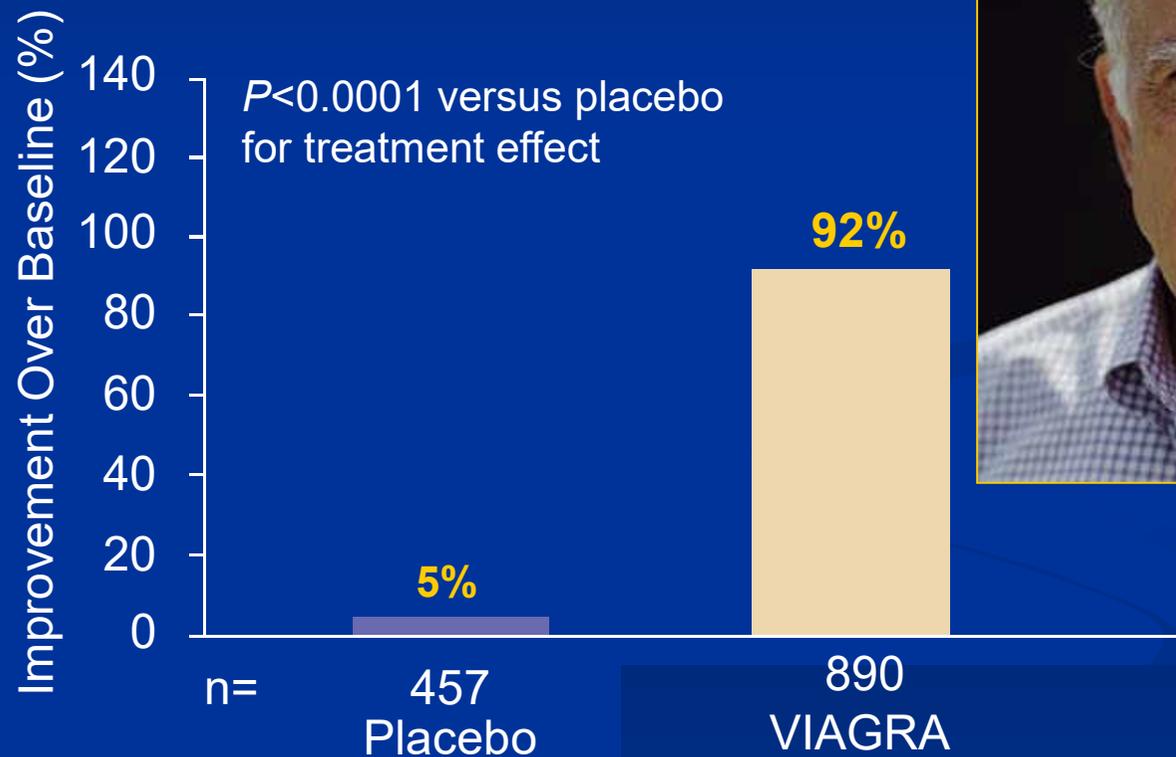
Improvement in Ability to Have Intercourse in Patients With **Spinal Cord Injury**



1. Holmgren E, et al. *Neurology*. 1998; in press.

Efficacy in **Elderly Patients**

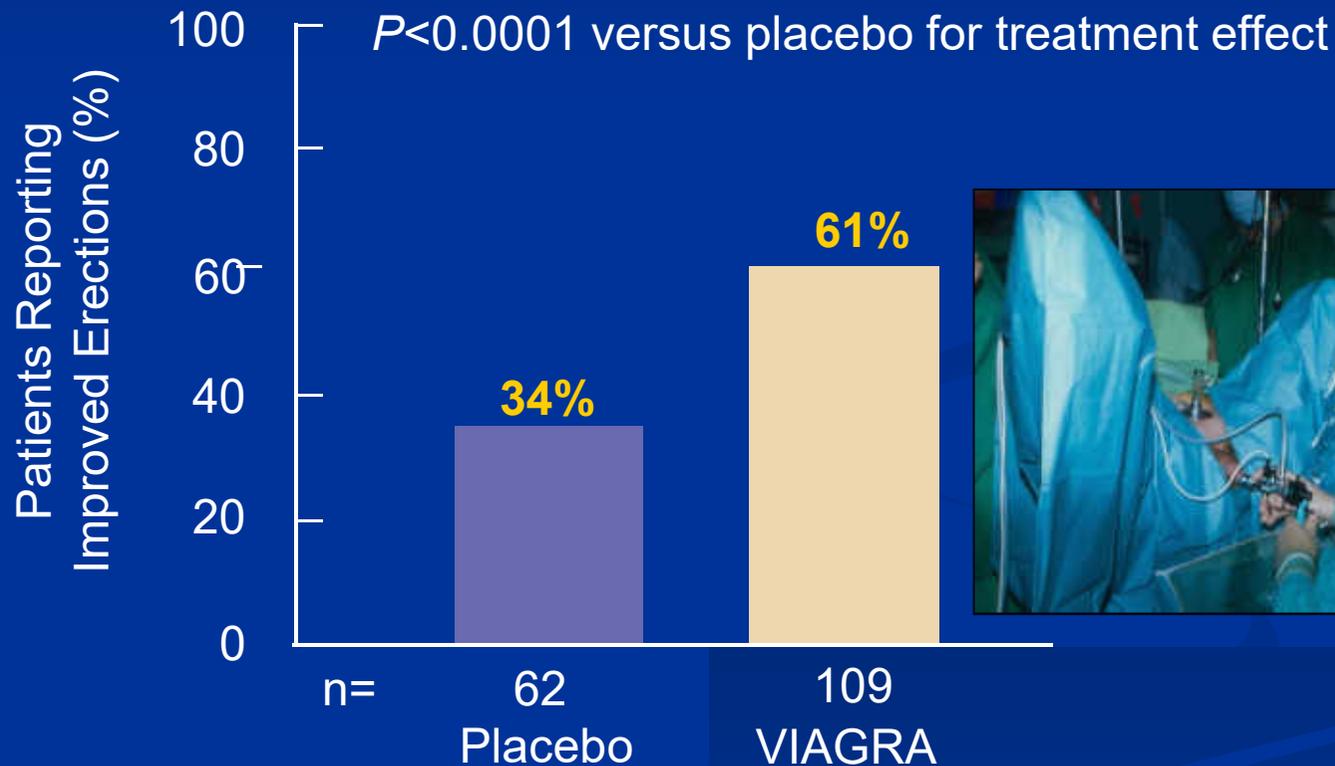
Ability to Achieve an Erection



Patients ≥ 65 Years of Age

Auerbach S, et al. *J Amer Ger Soc.* 1998;

Improvement in Erections in Patients Treated With **TURP**



Data on file, Pfizer Inc.

PDE-5-Inhibitors: Onset and Duration of Effect

PDE 5-Inhibitor	Onset of Effect	Duration of Effect
 Vardenafil	10 Minutes ¹	up to 12 hours ²
 Tadalafil	16 Minutes	24-36 hours
 Sildenafil	14 Minutes	4-8 hours

1 Montorsi et al. J Sex Med 2004; 1: 168-178

2 Porst et al. MMW 2005

PDE5 Inhibitors

Pharmacokinetic Parameters

	Vardenafil ¹	Sildenafil ²	Tadalafil ³
	20 mg	100 mg	20 mg
t_{\max} , h	0.8	1.16	2.0
$t_{1/2}$, h	4.7	3.82	17.5
C_{\max} , $\mu\text{g/l}$	31.8	327	378
AUC, $\mu\text{g}\cdot\text{h/l}$	96.3	1963	8066



Data derived from separate studies, values shown as means

¹Klotz et al, *Pharmacotherapy*, 2002, 22:418

²Sildenafil product monograph

³Porst, *IJIR*, 2002, 14 (Suppl 1): S57-S64

Adverse events of PDE5 Inhibitors

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision (PDE6)	1.9%	–	<2%
Back pain (PDE11)	–	6.5%	–
Myalgia	–	5.7%	–

Data are from the European Medicine Evaluation Association statements on product characteristics.

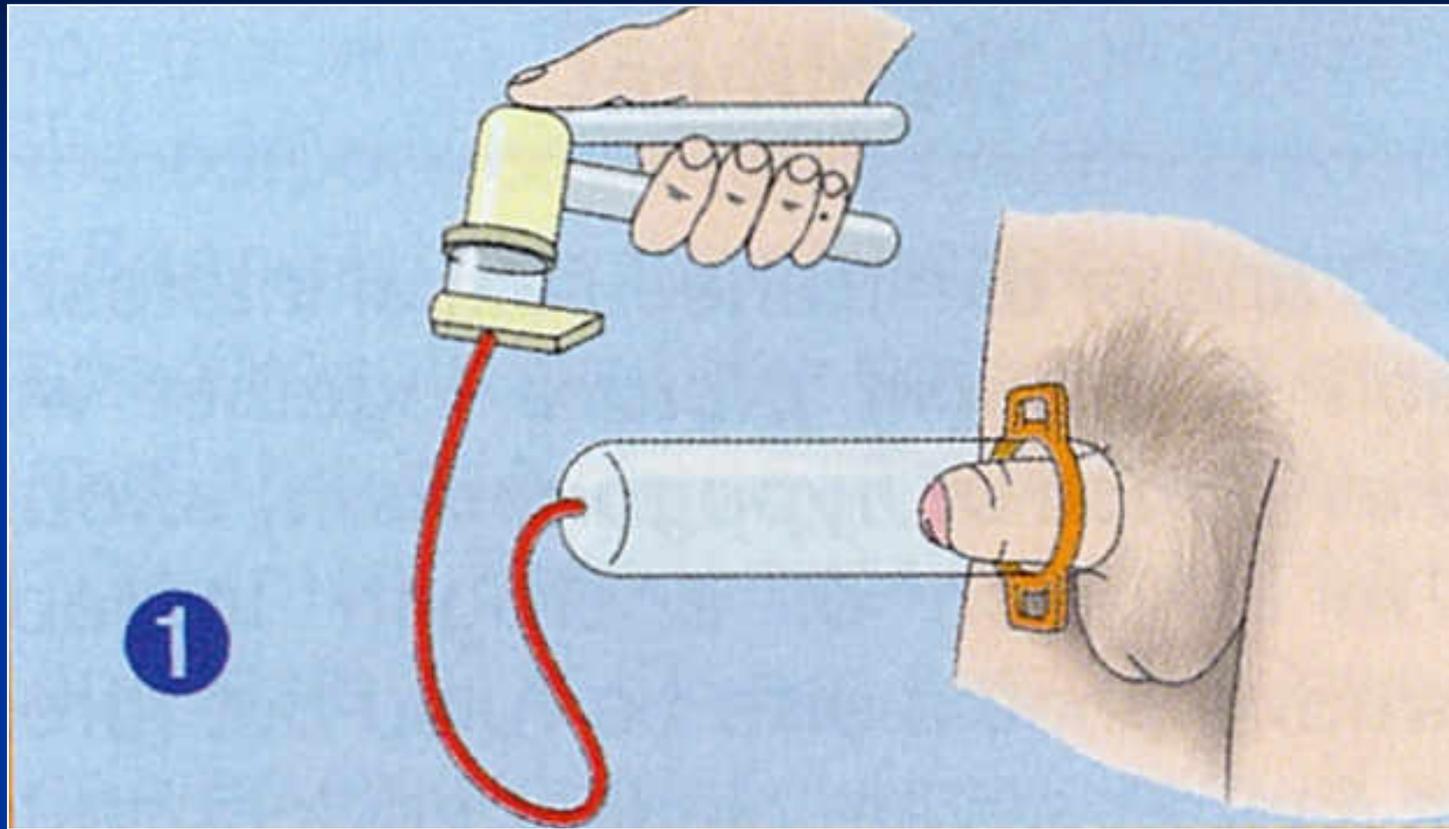


Contraindications



- Administration of PDE5 inhibitors to patients who use **nitric oxide donors or nitrates in any form is contraindicated.** Consistent with its known effects on the nitric oxide/cGMP pathway, PDE 5 inhibitor has been shown **to potentiate the hypotensive effects of nitrates.**
- Also contraindicated in patients with known hypersensitivity to any component of the tablet.

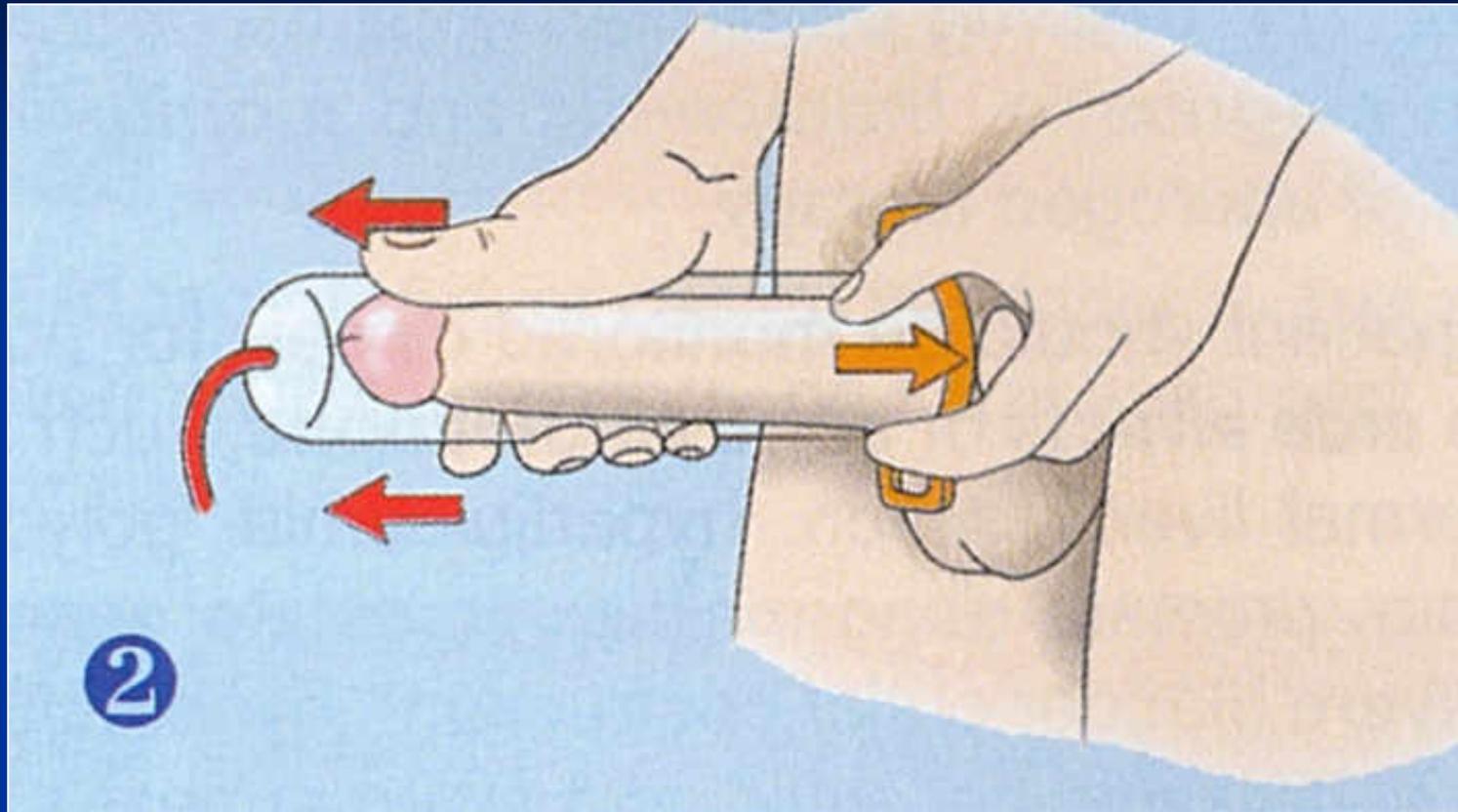
Vacuum tumescence device (VTD)



The cylinder is placed over the penis and held firmly against the pubis to obtain an airtight seal.

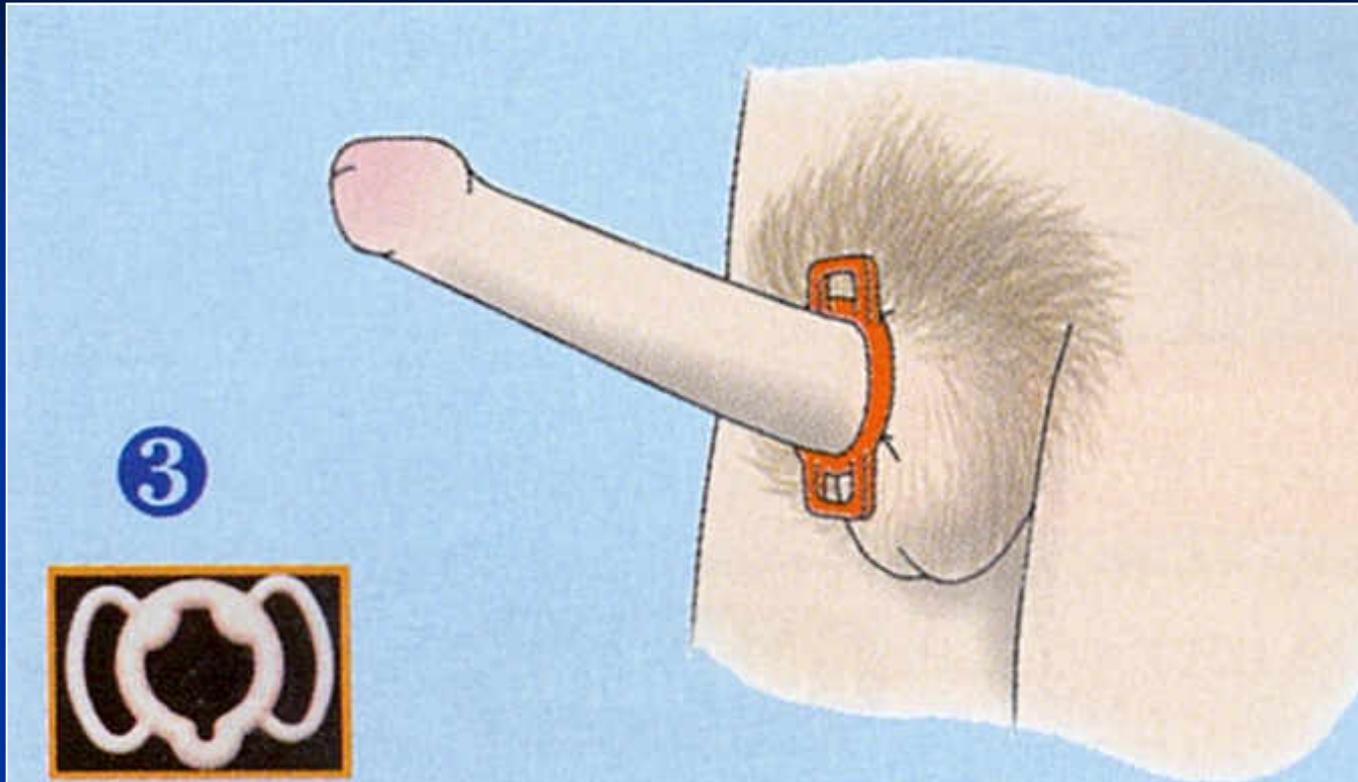
Suction is then applied to the vacuum pump to produce a **negative pressure** leading to **engorgement of the penis**

Vacuum tumescence device (VTD)



After the erect state is achieved a **constriction ring** is slipped from the cylinder onto the base of the penis **to maintain the erection**

Vacuum tumescence device (VTD)



The vacuum is then released via a valve and the cylinder removed.

Time to achieve erection is ~ 2-3 min.

The ring should not be left on for **more than 30 min!!!**

Advantages: noninvasive, effective for all etiologies

Disadvantages: cumbersome, requires good manual dexterity, coldness of penis, bruising, ejaculatory block

Intracavernosal injection therapy (IC)

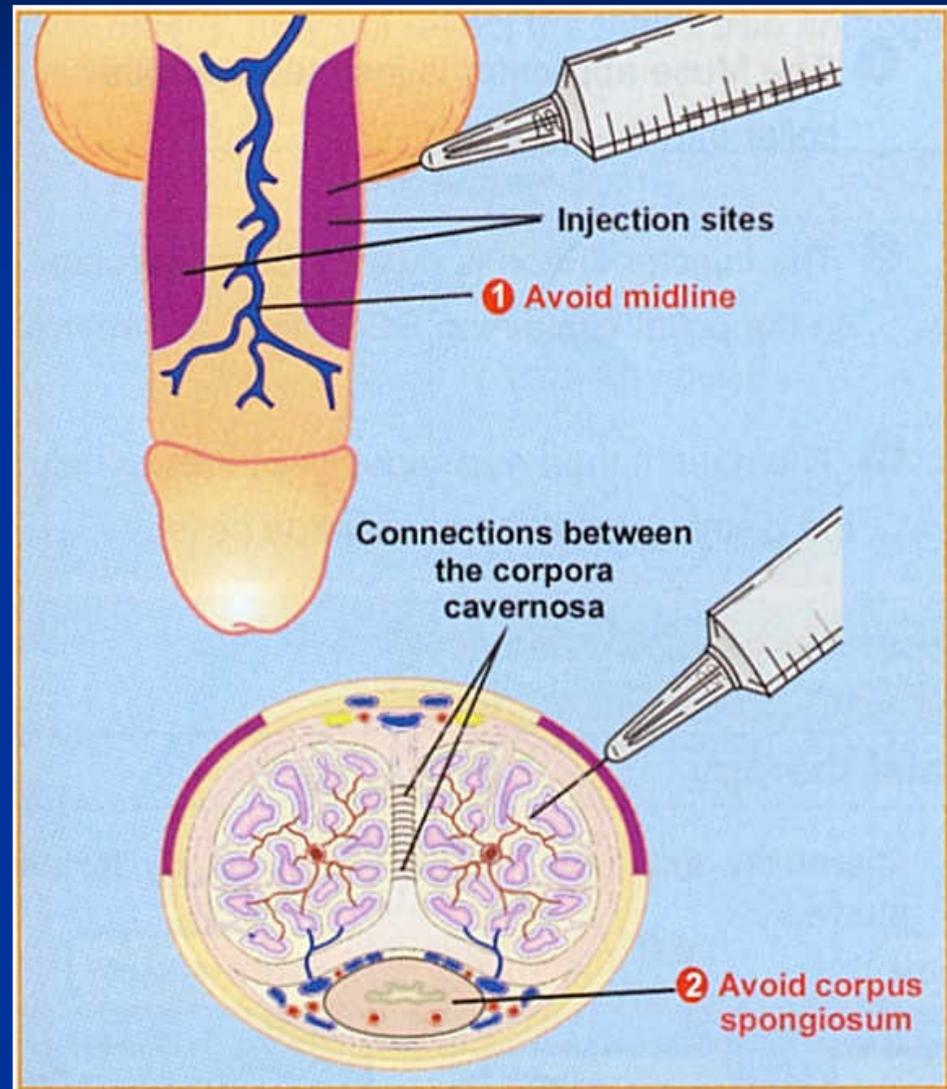
Before the PDE5 inhibitor's era the IC th. was a milestone in the treatment of ED.

It was the first time that a safe and highly effective pharmacologic treatment was available for many.

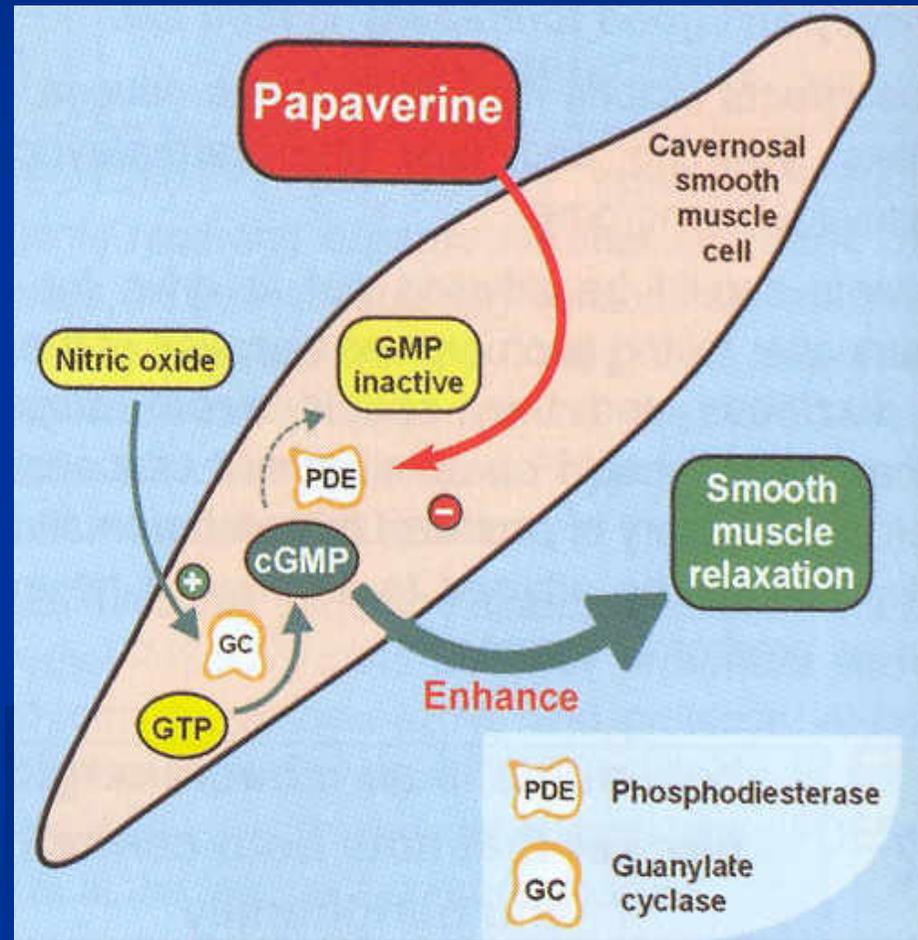
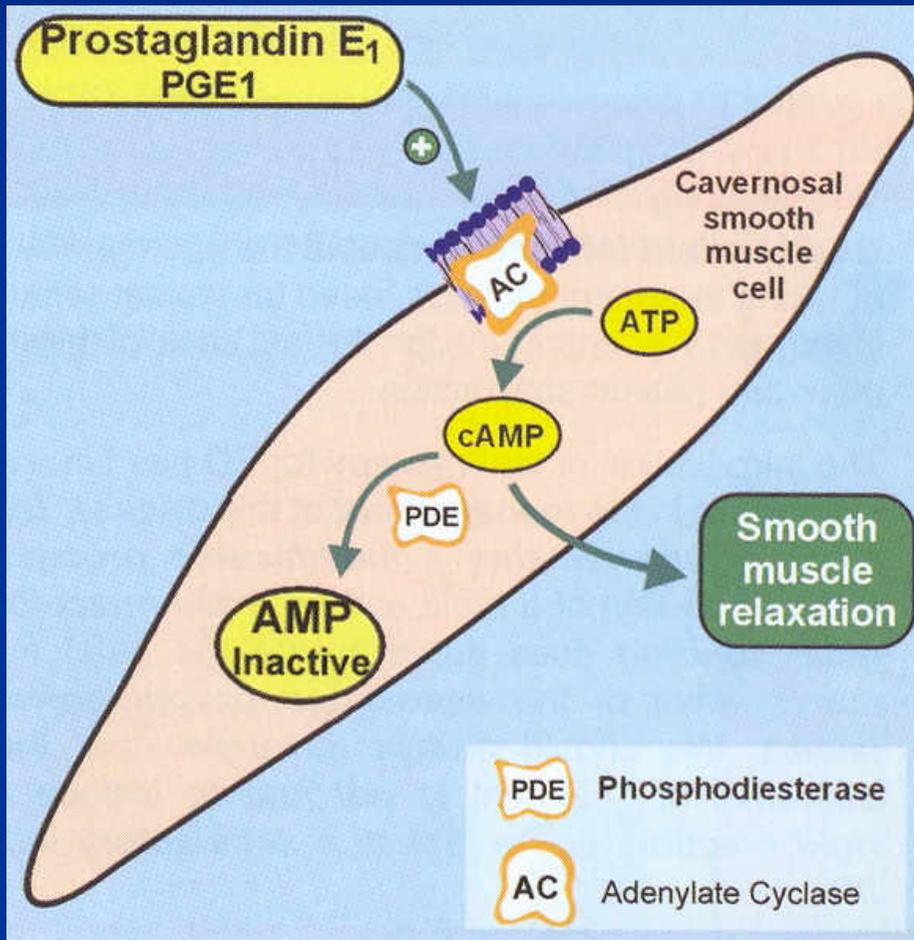
Virág mid 70's

PGE1 is the most widely used single agent
Papaverine and phentolamine are now rarely used alone but mainly in combination.

BIMIX
TRIMIX



The Intracellular Effect of **PGE1** and **Papaverine**



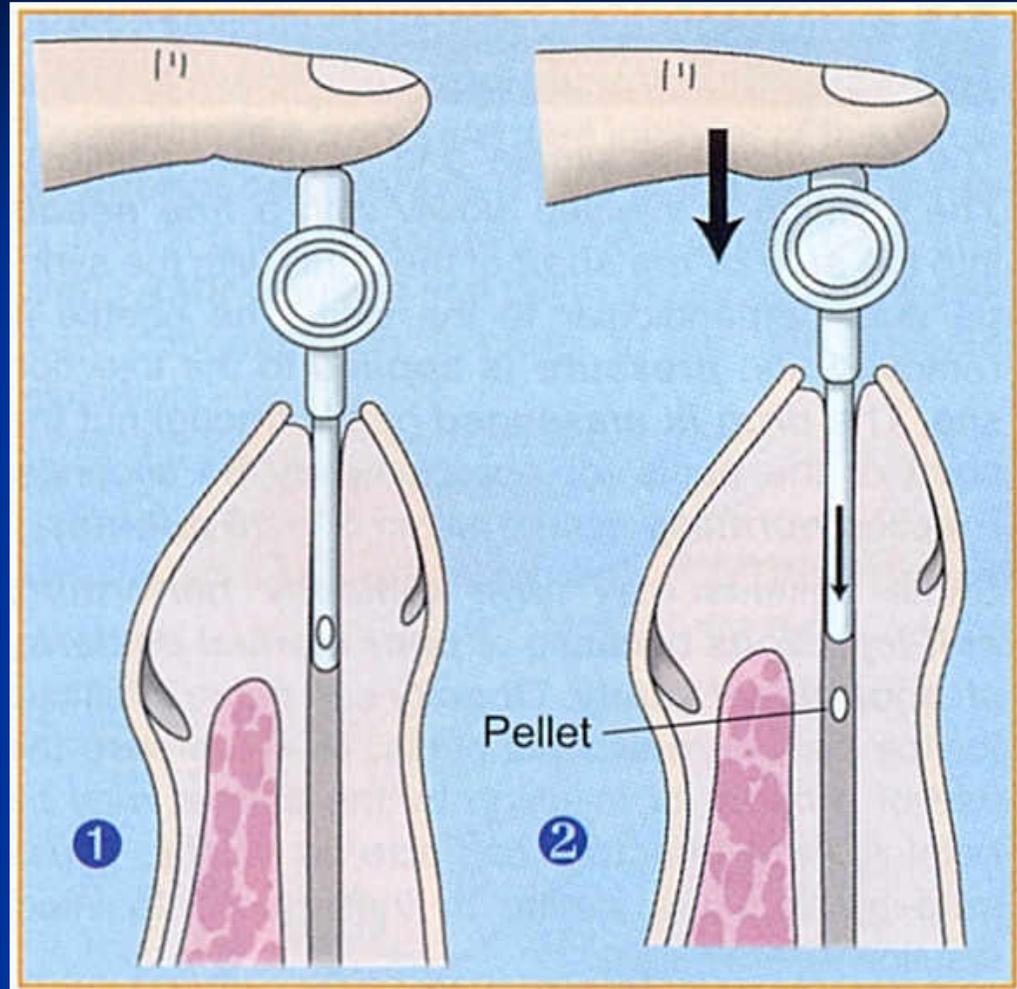
Intraurethral therapy

The urethral mucosa is permeable to drugs.

ALPROSTADIL (PGE₁)

in the form

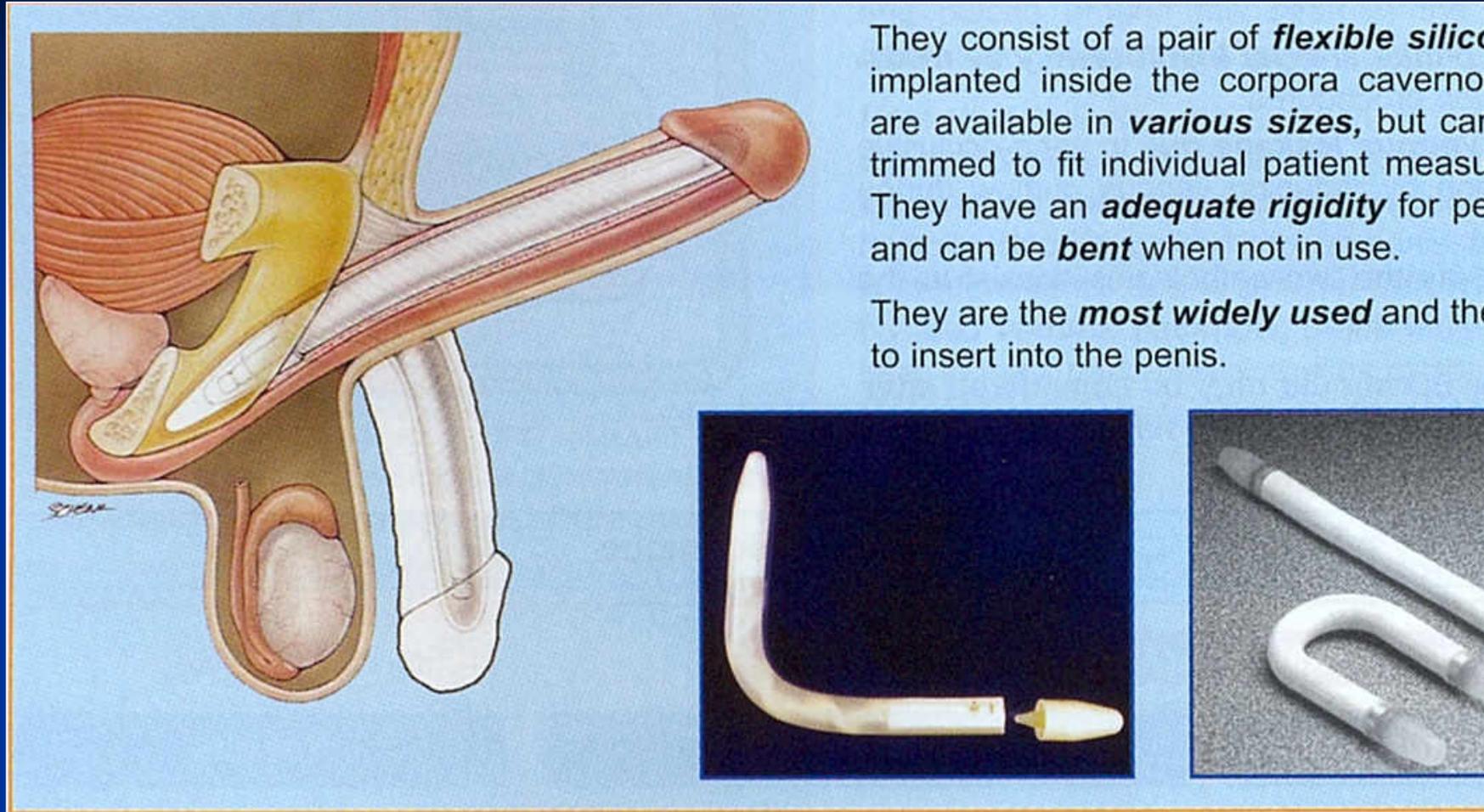
of a **small pellet** can be administered into the urethra via an administration system: **MUSE** (medicated urethral system for erection)



Advantages: no injection required

Disadvantages: intolerance due to penile pain, urethral bleeding and pain, variable efficacy (45%)

Malleable penile prostheses

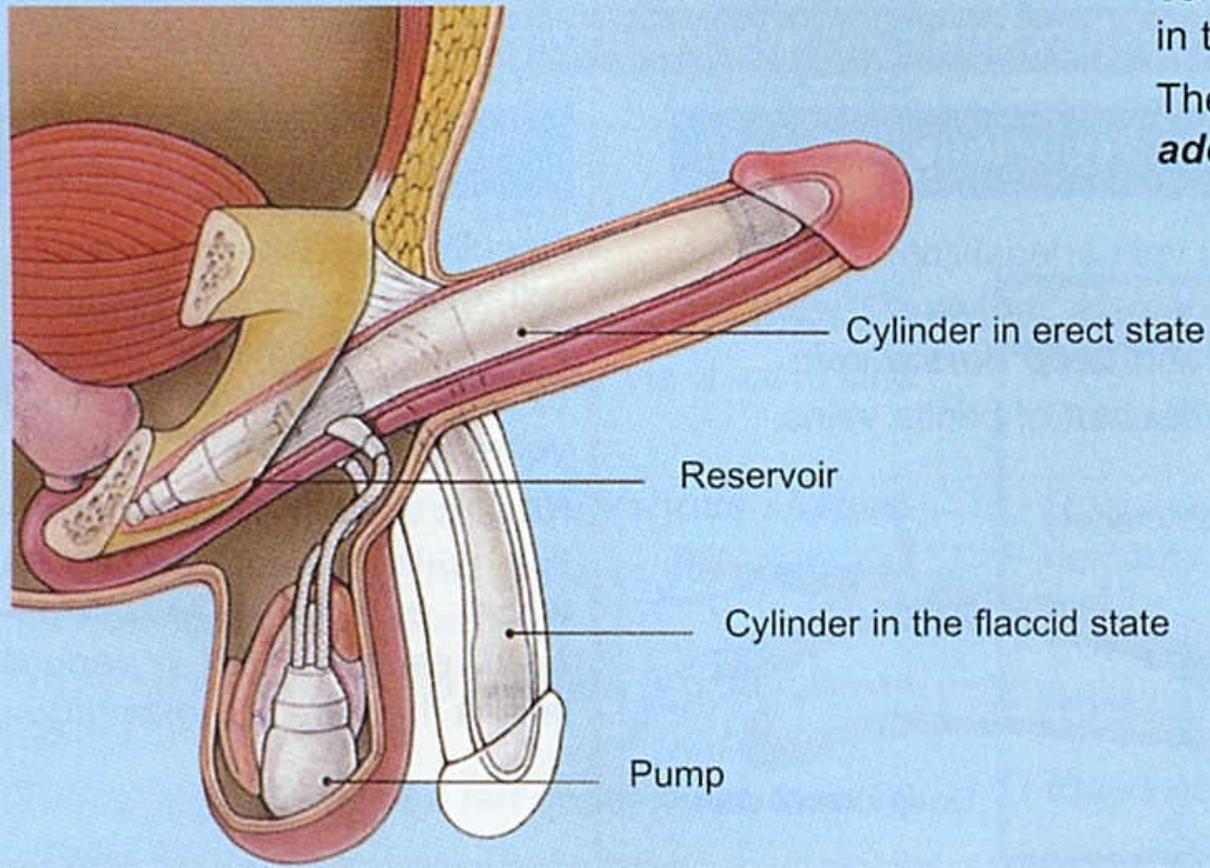


They consist of a pair of **flexible silicone** implanted inside the corpora cavernosa. They are available in **various sizes**, but can be trimmed to fit individual patient measurements. They have an **adequate rigidity** for penetration and can be **bent** when not in use.

They are the **most widely used** and the easiest to insert into the penis.

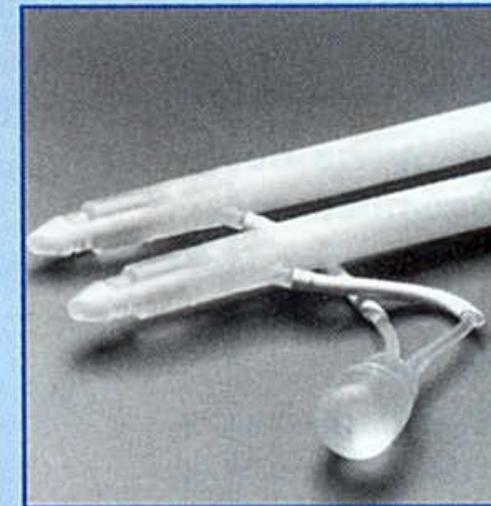
Penile prostheses are the **last resort** therapy, when all other means have **failed or are contraindicated**.

Two sorts of prostheses → **malleable** and **inflatable** devices.

A**TWO-PIECE INFLATABLE DEVICES**

They consist of *two inflatable cylinders* inserted into the corpora cavernosa, connected to a *pump-reservoir* in the *scrotum*.

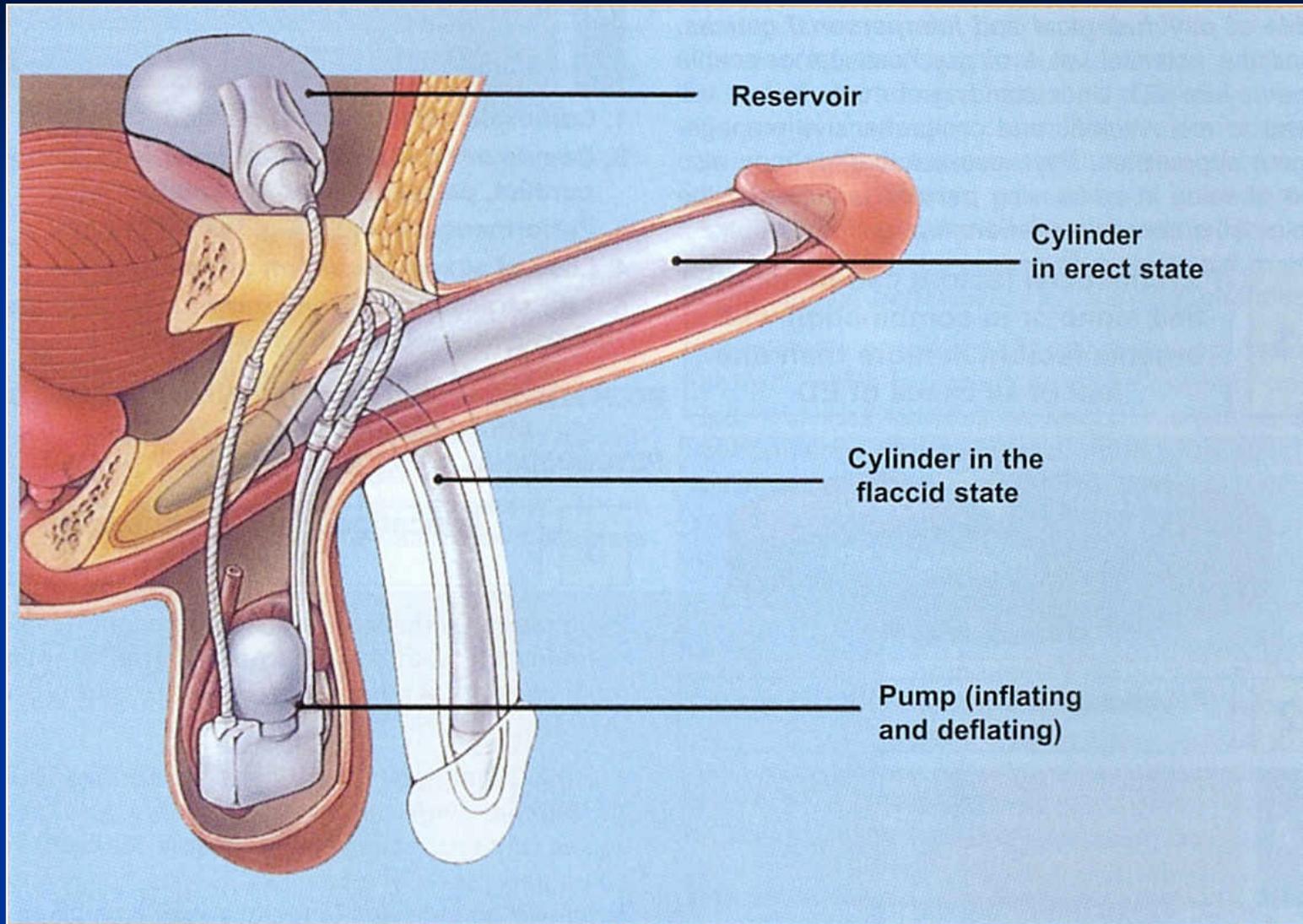
The relatively large reservoir ensures *adequate rigidity* and *flaccidity*.



P.proth. Complications: pain, infection (1-5 %), mechanical failures (less than 5 %)

Results: satisfaction rates from 66% to 92% for patients, 60%-80% for partners !!!

3-piece inflatable devices



They are **more complex to insert**, but give more satisfactory result.
Excellent erect and flaccid states with good cosmetic results during flaccidity

Erectile Dysfunction

Conclusions



- Erectile dysfunction is a **common condition**.
- A **nitric oxide-cGMP mechanism** plays a predominant role in mediating corpus cavernosal smooth muscle relaxation and penile erection.
- Erectile dysfunction **is associated with age** but is not an inevitable consequence of aging.
- **ED (early detection) of ED (erectile dysfunction) can save lives !!!**

Thank you for your attention !



Diagnosis of ED **may uncover** other serious treatable disorders

■ Hypertension

- 68% of men with hypertension had **ED** to some degree

■ Dyslipidemia

- 60% of men with **ED** had dyslipidaemia

■ Heart disease

- 56% of men with **ED** were found to have a positive stress test
- 40% of men with **ED** had significant coronary occlusions

Burchardt M et al. J Urol 2000; 164: 1188–1191

Billups K, Friedrich S. Presented at AUA, May 2000; Atlanta, Ga

Pritzker MR. Circulation 1999; 100 (18): I-711

Levine L, Kloner R. Am J Cardiol 2000;86:1210-13

ED: take the lead !



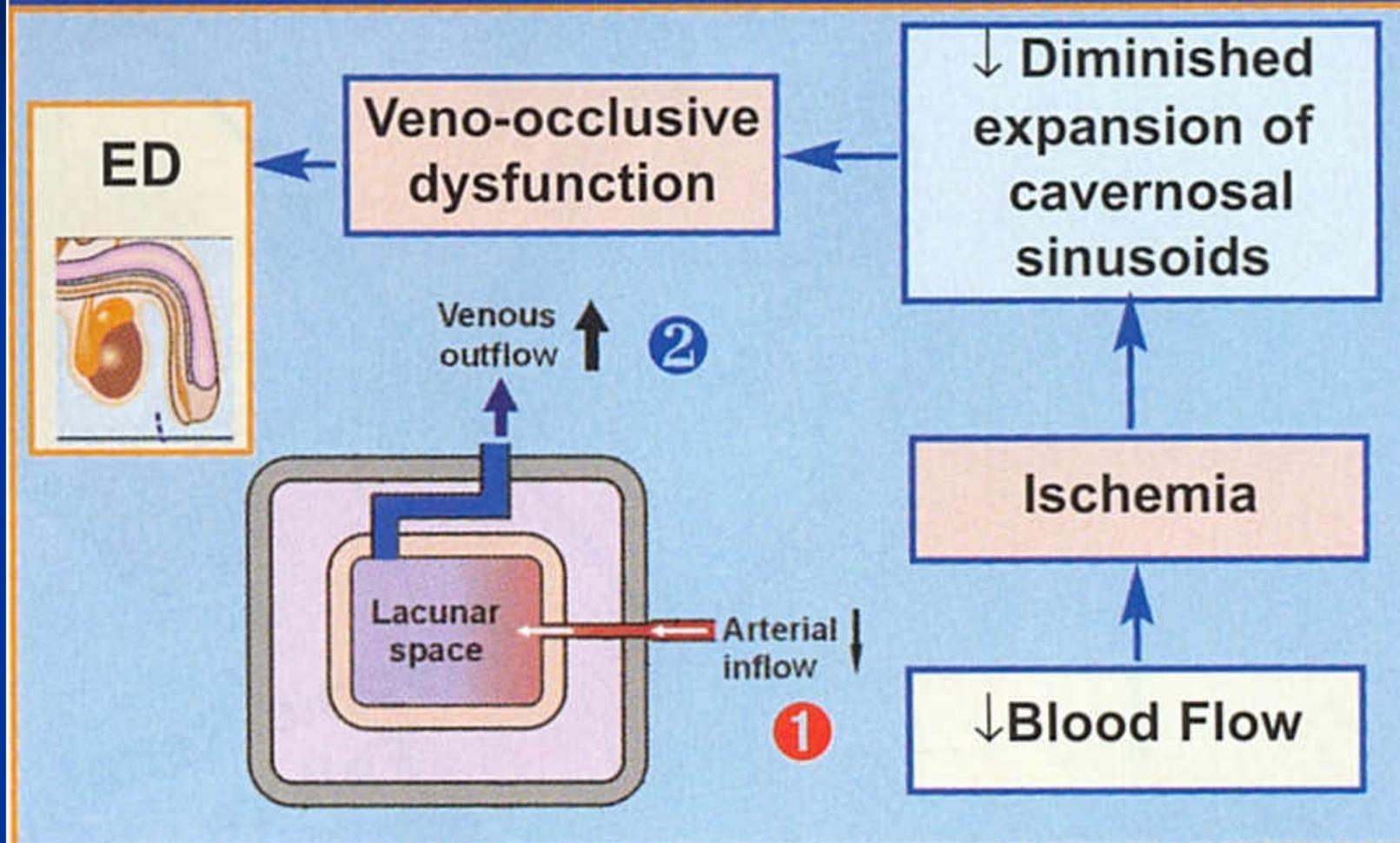
The Types of Vasculogenic ED

- **ARTERIOGENIC** – with reduced arterial inflow
- **VENOGENIC** – with dysfunction of the veno-occlusive mechanism



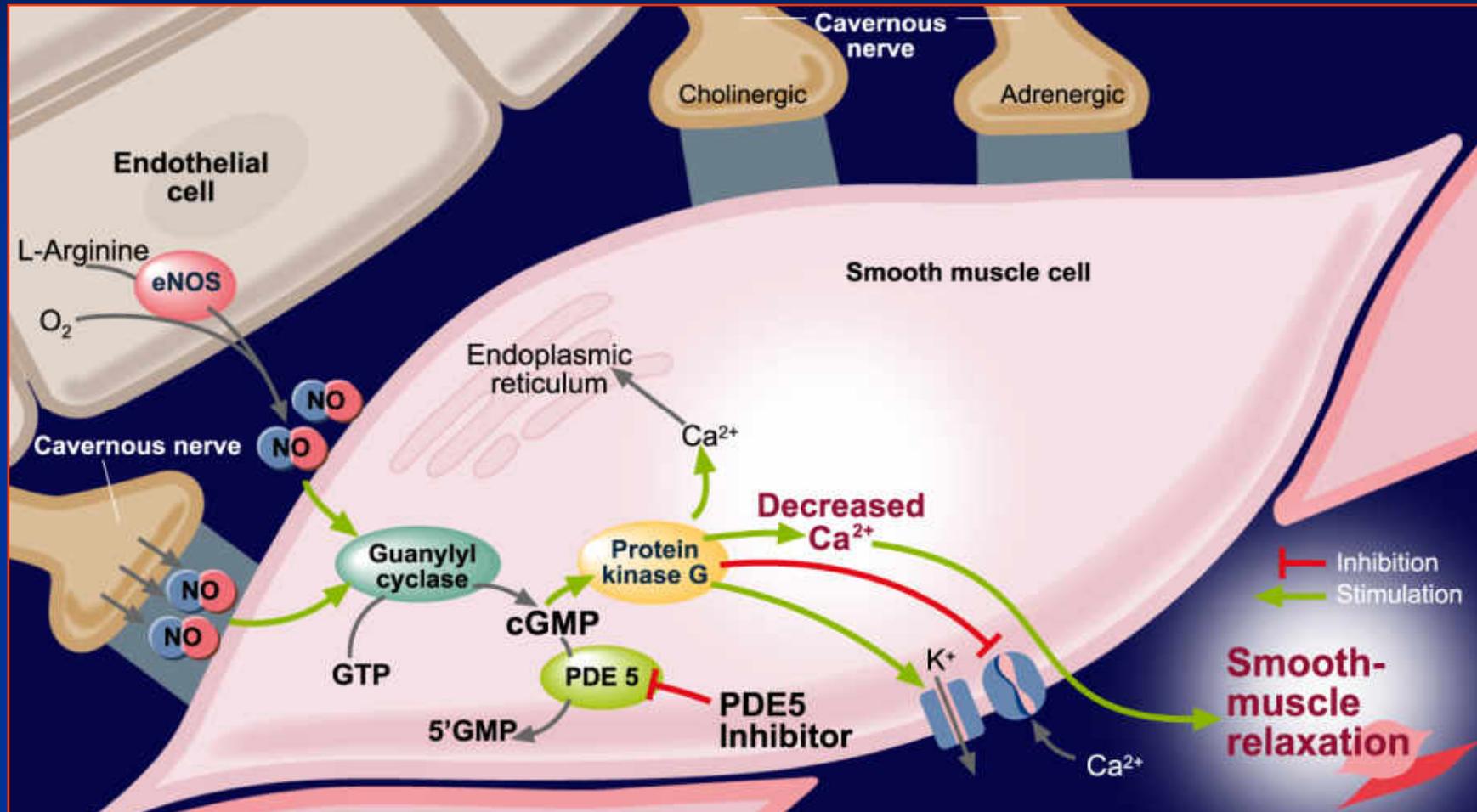
- In practice, the **two mechanisms are associated** in the great majority of cases

Effect of Ischemia on Cavernosal Sinusoids



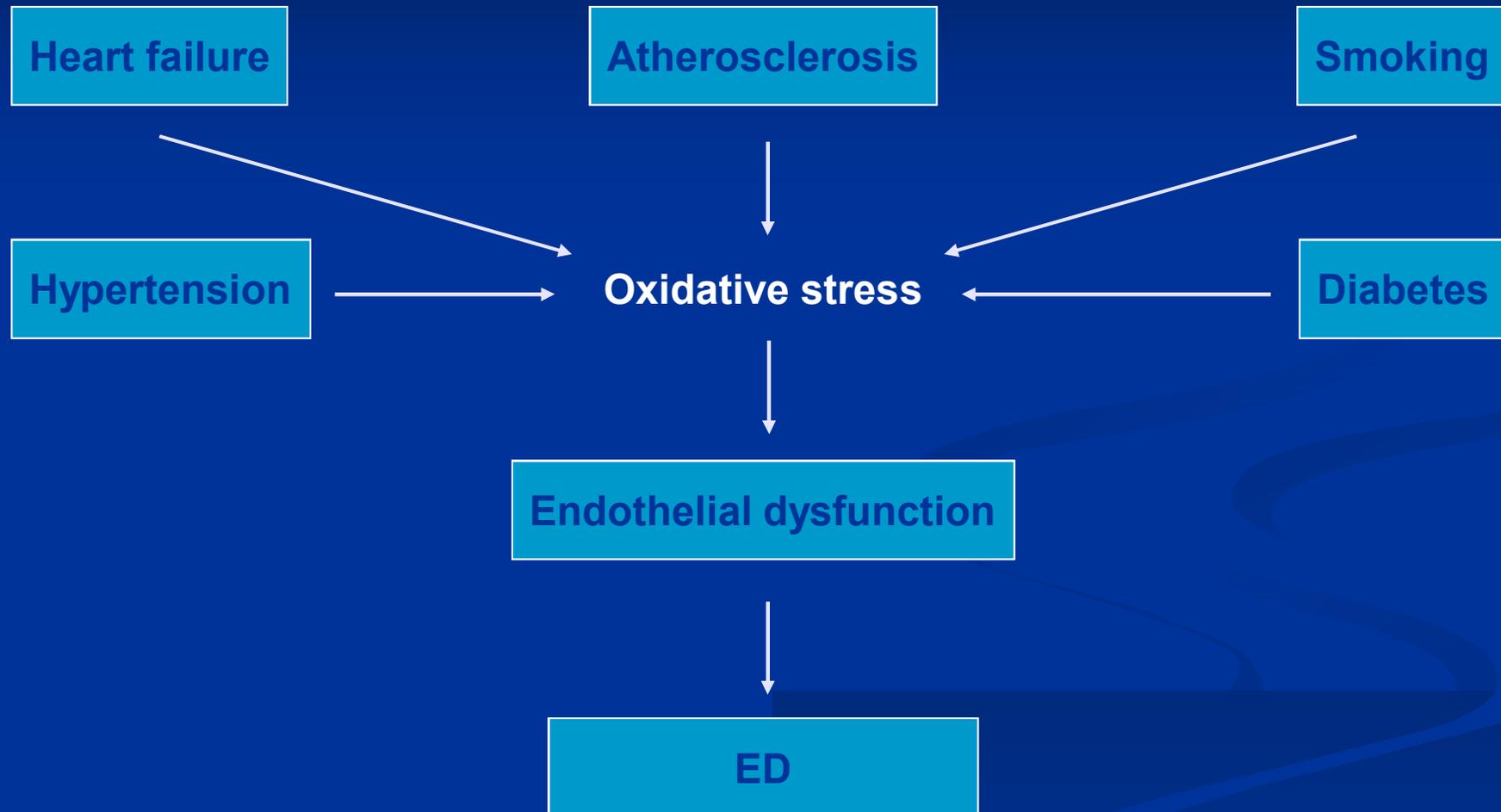
In the long run **ischaemia** induces loss of smooth muscle **fibers and fibrosis**, which further decreases the **compliance** of the structures.

MODE OF ACTION



Lue T. *N Engl J Med* 2000; 342: 1802–13.

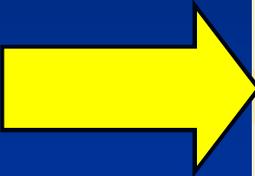
Endothelial dysfunction is a risk factor for **CVD** and **ED**



Adapted from Rubanyi GM. J Cardiovasc Pharmacol 1993; 22 (Suppl 4): S1–S4

Table 1

Comparison of the phosphodiesterase-5 inhibitors



Property	Sildenafil citrate (Viagra)	Vardenafil HCl (Levitra)	Tadalafil (Cialis)
Usual dosage*	50 or 100 mg 1 h before sexual activity	10 or 20 mg 1 h before sexual activity	10 or 20 mg before sexual activity
Onset of action	16-27 min	20 min	16 min
Duration of action	8 h	8 h	36 h
Half-life	3-4 h	3-4 h	18 h
Food interactions	High-fat foods delay effects	High-fat foods delay effects	No effects
Side effects	Headache, facial flushing, nasal congestion, dyspepsia, visual disturbances	Headache, facial flushing, nasal congestion, dyspepsia, visual disturbances	Headache, facial flushing, nasal congestion, dyspepsia, back and muscle pain
Drug interactions	Contraindicated in patients taking nitrates Do not administer doses >25 mg within 4 h of taking alpha-blocker Reduce dosage to 25 mg in patients taking potent CYP3A4 inhibitors [†]	Contraindicated in patients taking nitrates or alpha- blockers Limit dosage to ≤2.5 mg q 72 h in patients taking potent CYP3A4 inhibitors [†]	Contraindicated in patients taking nitrates or alpha- blockers (except for 0.4-mg dose of tamsulosin HCl [Flomax]) Limit dosage to ≤10 mg q 72 h in patients taking ritonavir (Norvir); use 2.5 or 5.0 mg q 24 h in patients taking other potent CYP3A4 inhibitors [‡]

*See Table 2 for dose adjustment in patients with renal or hepatic disease.

[†]Potent CYP3A4 inhibitors include protease inhibitors, erythromycin (eg, E-Base, E-Mycin, Ery-Tab), and itraconazole (Sporanox).

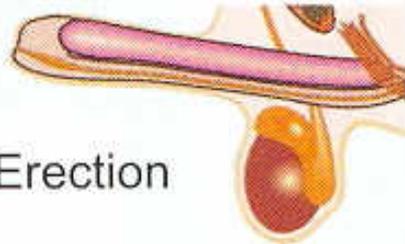
[‡]The 2.5 or 5.0 dose of tadalafil is used with itraconazole, ketoconazole (Nizoral), and indinavir sulfate (Crixivan).

Androgenic Action

Libido



Erection



Mainly nocturnal erections

To a certain extent
Mainly nocturnal erections



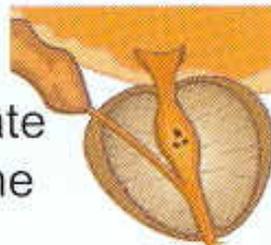
Secondary sexual characteristics



Body hair and skin changes



Prostate volume



Up to a certain limit

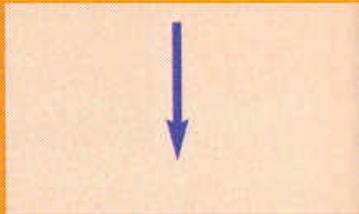


PSA and volume

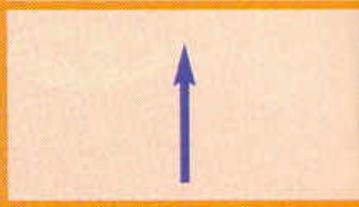
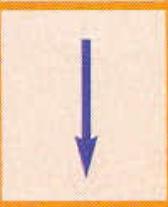


Anabolic Action

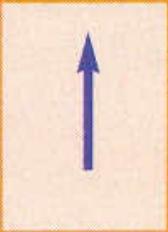
Muscle mass 



Fat mass 



Erythropoiesis 



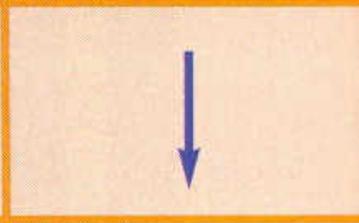
Anemia 

Bone mineral density 

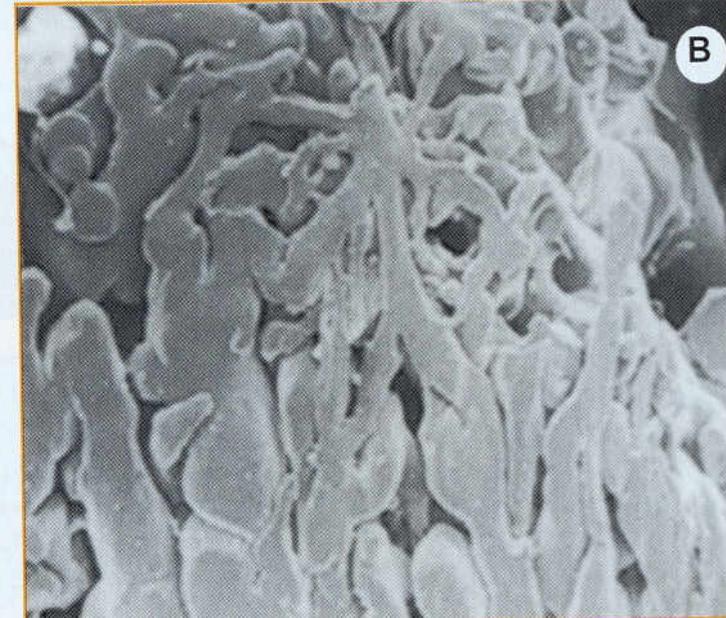
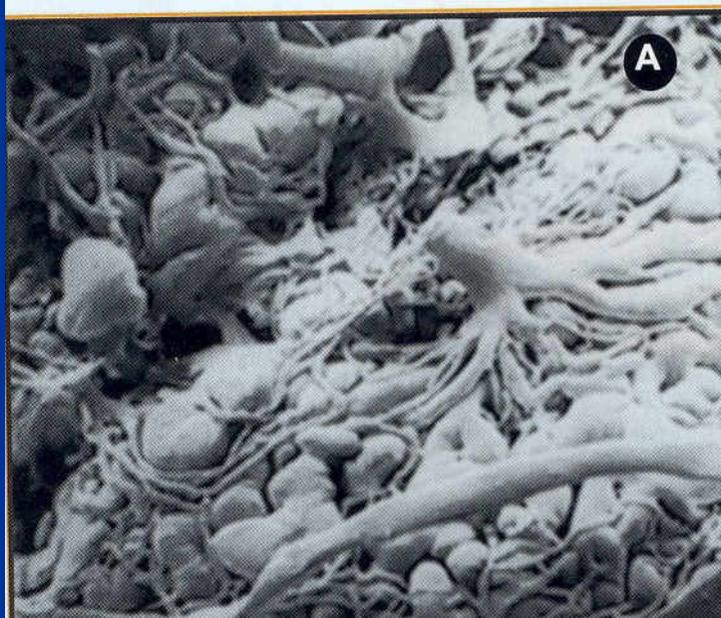
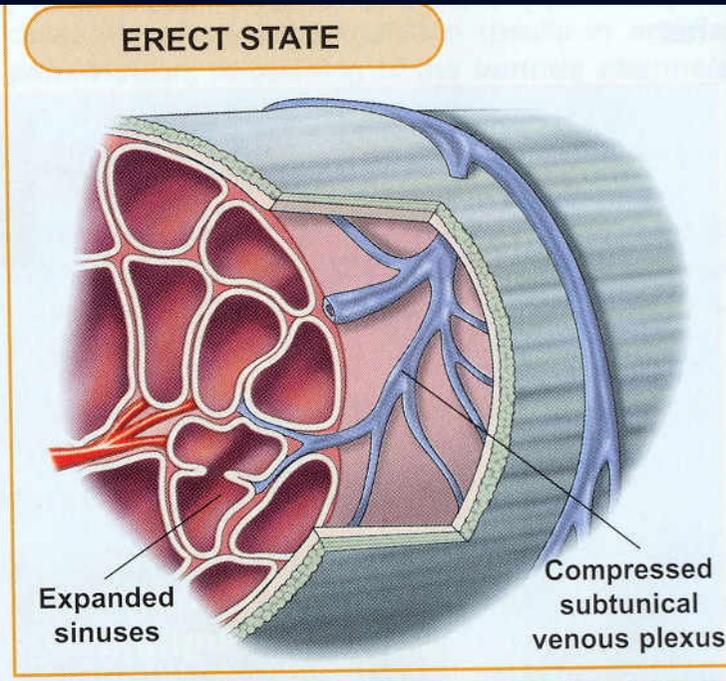
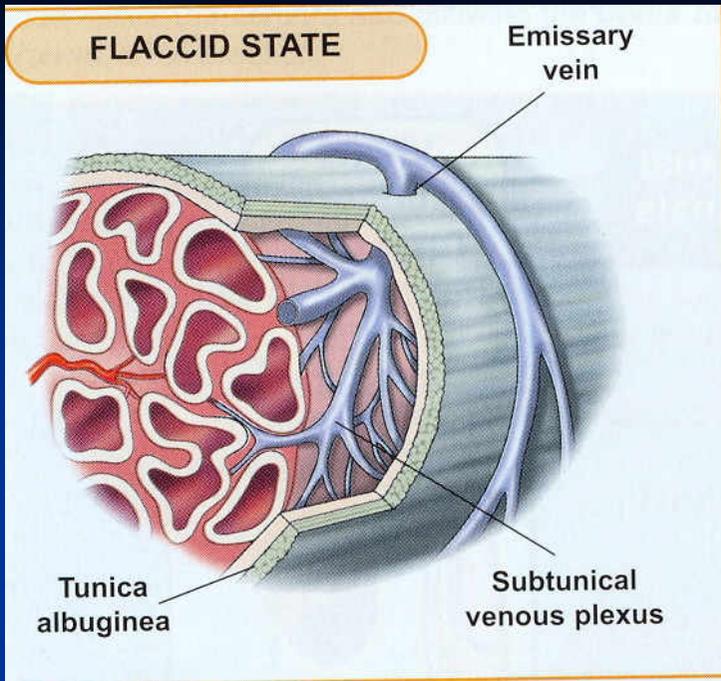


Osteoporosis 

Cognitive function and general well-being 



Hot Flashes



Treatment of Erectile Dysfunction

Suggested Characteristics of an Ideal Therapy

- Simple
- Non-invasive
- Non-painful
- High success rate
- Few minor side effects



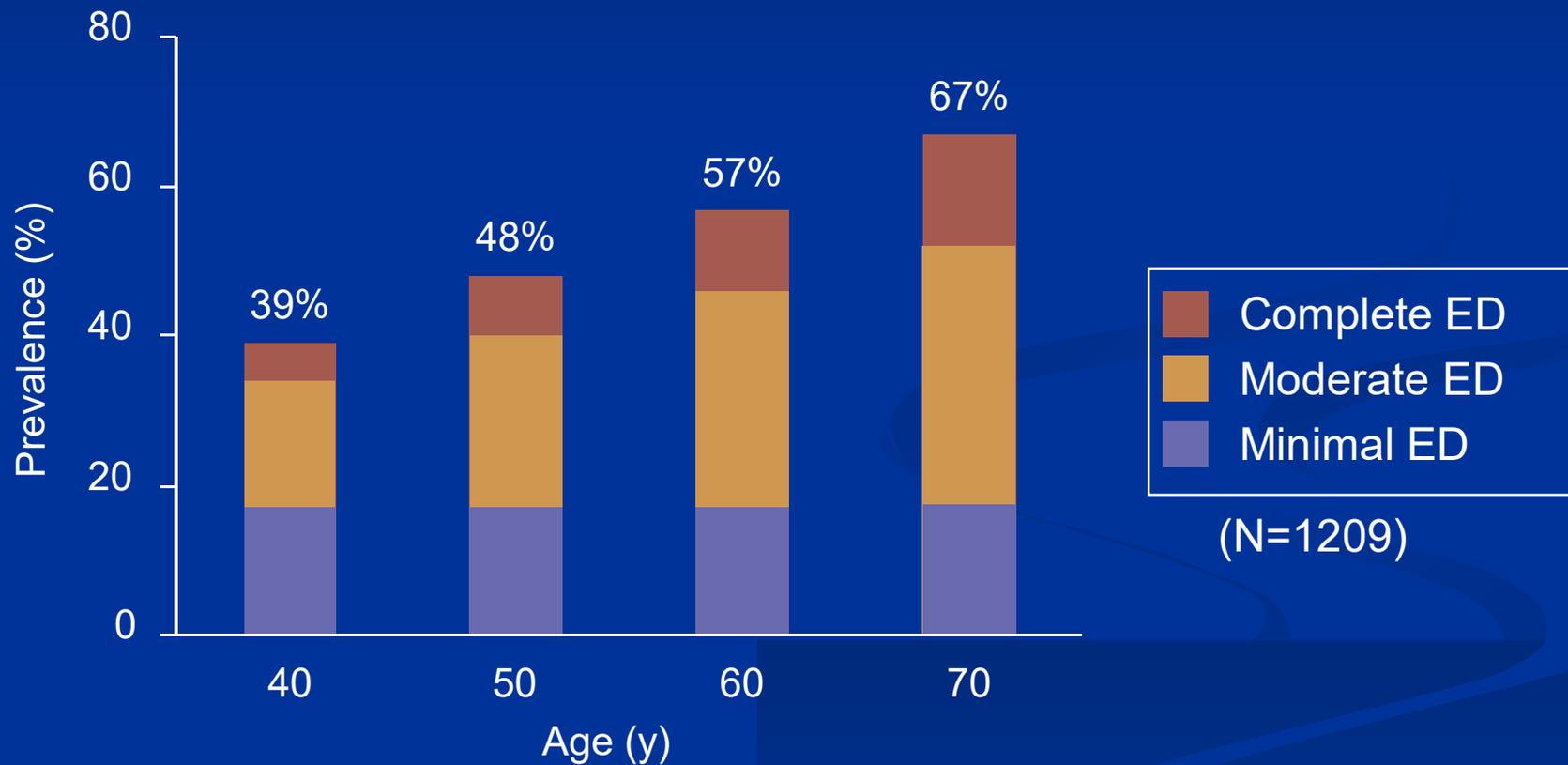
Talking about ED: what the **patient** wants

- From 500 adults aged 25 years and older
 - 91% of married men ranked a satisfying sex life as important
 - 68% were afraid that physicians would be embarrassed if they talked about ED
 - 71% believed doctors would dismiss concerns about sexual problems
 - Patients wait >5 years after ED symptoms to visit a physician

Erectile Dysfunction

Age & Prevalence

Massachusetts Male Aging Study¹

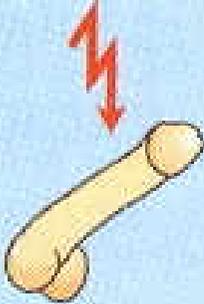
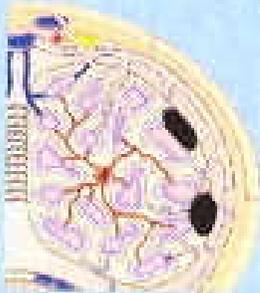


1. Feldman HA, et al. *J Urol.* 1994;151:54-61.

Francois Gigot de
La Peyronie



SIDE EFFECTS

	Pain	Fibrosis	Priapism
			
PGE1	15%	1.7%	1%
Bimix	1%	7%	7%
Trimix	5%	7%	10%

Bimix (papaverine + phentolamine)

Trimix (papaverine + phentolamine + PGE1).

Phentolamine alone has a modest therapeutic effect. It has a **synergistic action** with other drugs due to **blocking the sympathetic neuronal activity**.

ED: facts and figures

- ED is **extremely common**

- it affects an estimated more than **30 million** men only in the **U.S.** to some degree



- ED is **under-treated**

- less than 2 in 10 men with ED are being treated
- 8 of 10 men want their doctor to ask them about ED

NIH Consensus Development Panel. JAMA 1993; 270: 83–90
Mulcahy JJ. J Urol 2000; 163: 471
Baldwin KC. J Urol 2000; 163 (Suppl): 243 Abstract 1080



Talking about ED: what the **patient** wants

- From 500 men with **ED** visiting a **urologist**
 - Only 22% reported discussing the problem with their **primary care (or other) physician**
 - 8 of 10 said they would have liked their physician to initiate a discussion on **ED during routine visits**



That's why are we here!!!

The LEVITRA Challenge
Is As Easy As 1 2 3

1. Talk with your doctor about
your ED symptoms

START THE CHALLENGE NOW

SOUND: ON | OFF

LEVITRA
Tadalafil HCl
Challenge