ERECTILE DYSFUNCTION PATIENTS IN INSTITUT UROLOGI & NEFROLOGI (IUN), HOSPITAL KUALA LUMPUR (HKL) AND CLINICAL TRIAL WITH TRANSURETHERAL ALPROSTADIL (MUSE®)

BY

DR NOOR AZAM BIN NASUHA

MBBS (MALAYA)

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II. ABSTRACT

The aim of this study was to evaluate the factors contributing towards erectile dysfunction (ED) in patients followed-up in the Institut Urologi & Nefrologi, Hospital Kuala Lumpur between 1st. March 1999 to 31st. August 1999. One hundred and fifty-four patients were included in this study. The mean age of the patients was 52.68 years. The youngest was 22 and the oldest was 76 year-old. Most were between the age of 45 and 65 year-old.

Diabetes mellitus and hypertension played a major role as contributing factors in the overall study population. 45.4% of the patients have diabetes mellitus and 29.2% have hypertension. 41.5% of the patients have single contributing factor towards erectile dysfunction whereas 29.2% have two and 10.4% of the patients have three contributing factors. In 18.2% of the studied patients the cause of ED were unknown. In term of racial distribution, Malays contributed 48.7% of the study sample; Indian 25.3% and Chinese constitute about 22.1%.

35 patients who fulfilled the inclusion criteria were enrolled in the clinical trial with transurethral alprostadil (MUSE®). Thirty patients (85.6%) completed the in-clinic titration phase. Of these, 18 patients (60%) responded well to the MUSE® and they were sent home with the medication. However only 33.3% of patients completed the home phase.

In conclusion, diabetes mellitus plays an important role in our patients with erectile dysfunction and MUSE® is one of the alternative treatment for such condition.

III. ABSTRAK

Tujuan penyelidikan ini adalah untuk menilai factor-faktor yang menyumbang ke arah 'erectile dysfuction' atau pemyakit mati pucuk di atas pesakit-pesakit yang dirawat di Institut Urologi dan Nefrologi, Hospital Kuala Lumpur di antara 1hb Mac hingga 31hb Ogos, 1999. Seramai seratus limapuluh empat pesakit terlibat dalam penyelidikan ini. Purata umur pesakit adalah 52.68 tahun dengan yang termuda 22 tahun dan tertua 76 tahun. Kebanyakan daripada pesakit ini berumur di antara 45 dan 65 tahun.

Kencing manis dan darah tinggi memainkan peranan yang penting dalam keseluruhan sample penyelidikan. Seramai 45.5% menghidap kencing manis and 29.2% menghidap darah tinggi. Seramai 41.5% daripada pesakit=pesakit ini mempunyai satu factor yang menyumbang ke arah penyakit ini, 29.2% mempunyai dua factor penyumbang dan 10.4% dengan tiga factor penyumbang sementara 18.2% lagi tidak diketahui penyebabnya. Pesakit Melayu merangkumi 48.7% dari sample, sementara pesakit India seramai 25.3% dan Cina merangkumi 22.1%.

Tigapuluh-lima pesakit yang menepati syarat telah mengambil bahagian dalam kajian MUSE®. Tigapuluh pesakit (85.6%) menamatkan peringkat klinik. Lapanbelas daripadanya (60%) memberikan tindakbalas yang baik terhadap MUSE® dan seterusnya pulang dengan dos yang tertentu. Walaubagaimanapun hanya 33.3% daripada mereka menamatkan peringkat di rumah. Kesimpulannya, kencing manis memainkan peranan penting dalam pesakit kita ke arah menyumbang kepada penyakit 'erectila dysfunction'. MUSE®. Adalah salah satu rawatan alternatif kepada pesakit-pesakit ini.

V. LIST OF ABBREVIATIONS

ACTH	adrenocorticotrophin hormone
cGMP	3', 5'-cyclic guanosine monophosphate
CGRP	calcitonin-gene-related peptide
DICC	dynamic infusion cavernosometry and cavernosography
EAS	Erection assessment scale
ED	Erectile dysfunction
EEG	electroencephalography
EMG	electromyography
GABA	γ-amino-butyric acid
GTN	Glyceryl trinitrate
ICI	Intracavernous injection
IUN	Institut Urologi dan Nefrologi
HKL	Hospital Kuala Lumpur
MMAS	Massachusetts Male Aging Study
MPON	Medial preoptic nucleus
MSH	melanocyte stimulating hormone
MUSE®	Medicated urethral system for erection
NANC	nonadrenergic noncholinergic
NO	Nitric oxide
NOS	Nitric oxide synthase
NPT	Nocturnal penile tumescence
PGE1	Prostaglandin E1

PVN	Paraventricular nucleus
REM	rapid eye movement
VIP	Vasoactive intestinal peptide
5-HT	5-hydroxytryptamine

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VIII. ACKNOWLEDGEMENT

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IX. DEDICATION

I dedicate this dissertation to my late mother, Allahyarhamah Raja Maimunah Bt. Raja Ahmad, who was the first person that wished me to become a doctor. To my father, 'I want to make you happy'.

Last but not least, I wished to thank my wife, Nik Norliza Bt. Nik Hassan and my family for all their support and patience. To my sons, Mohd Danial Adha and Mohamad Noor Farhan, 'one day, you'll understand why I'm so busy now'.

1. INTRODUCTION

1.0 INTRODUCTION

Until a few years ago, what we now refer to as erectile dysfunction was often and erroneously called impotence. However, impotence has bad connotations. People relate sterility, premature ejaculation and a host of other sexual problem to the term. In 1992, the National Institute of Health Consensus Panel has defined erectile dysfunction as inability to achieve or maintain erection sufficient for satisfactory sexual function.[1, 2, 3] Historically, the prevalence of erectile dysfunction has been difficult to estimate due to the fact that it is not life threatening, and the patients often do not seek treatment.

However in 1948, a historical starting point for epidemiological data on the prevalence of erectile dysfunction started when Kinsey *et al* from United States did a study on 15,781 people whose age ranged from 10 to 80 years. He concluded that the prevalence of erectile dysfunction was less than 1% in people age below 30 years, less than 3% in people below 45 years, 6.7% between 45 to 55 years, 25% at 65 years and 80% at 80 years. However, these has to be interpreted with caution because out of 15,781 people, only 4108 were more than 25 year-old and only 306 were above 55.[3]

In 1990, Spector and Carey reviewed 23 studies done from 1948 till 1988 and he found that the prevalence of erectile dysfunction is between 4 to 9% in the community study.[3] Diokno *et al* (1990) said that prevalence of erectile dysfunction is 35% in people age above 60 years and it is significantly associated with heart attack, urinary incontinence and the use of sedatives.[3]

More recently, Feldman *et al* (1994) using the result of Massachusetts Male Aging Study from 1987 to 1989 on 1290 non institutionalized men age 40 to 70 years in 11

randomly selected cities in Boston, Massachusetts found that the prevalence of minimal, moderate and complete erectile dysfunction were 17%, 25% and 10% respectively. Base on this study, US population projection till 2005 estimated that there will be more than 50 million people age between 40 and 70 years and out of these, erectile dysfunction will affect 25 million people. There will be 39% of 40 years men and 67% of 70 year-old man with erectile dysfunction. In term of degree of erectile dysfunction, 5% of 40 year-old man and 15% of 70 year-old man will have complete erectile dysfunction. 17% of 40 year-old and 34% of 70 year-old man will have moderate erectile dysfunction and 17% of man age 40 and 70 will have minimal erectile dysfunction[4].

Jonler *et al* (1995) screened 1517 people age above 40 years and he found that 129 (8.5%) of them had no erection for the past 12 months. Out of 1,388 people, who have erection, 12.4% of them has erection in less than 1 in 5 times of sexual stimulation and 19.7% has erection in less than half the time. He also noted that the prevalence was significantly associated with age and lowered quality of life.[3]

However, only a few studies on prevalence of erectile dysfunction were done outside USA. In 1986, a small study on 109 people age more than 16 years in United Kingdom found that 32% of them had difficulty in achieving an erection and 20% had difficulty in maintaining an erection. Shirai *et al* (1987) from Japan noted the prevalence of erectile dysfunction was 26% and Solstad et *al* (1993) did a study on 411 Danish age 51 years and he found that the prevalence was 19%.[3]

Erectile dysfunction is a common disorder that most often occurs in association with diseases such as diabetes, hypertension, prostate cancer (as a consequence of surgery or anti-androgen therapy), vascular disease, neurological or spinal cord disease. While 40-90% of erectile dysfunction involves an organic component, psychological complications may contribute to or result from erectile dysfunction.

Although several treatments are available for erectile dysfunction, including vacuum erection devices, surgery (penile implant and vascular reconstruction), penile injection of vasoactive compounds, and recently introduced oral sildenafil; (Viagra) most patients still remain untreated. The threshold at which a man will seek treatment for erectile dysfunction has been high, because of social stigma and lack of convenient, safe and effective treatment. Previous studies conducted in the USA have shown that transurethral alprostadil, MUSE® which is a prostaglandin E1 is well tolerated and effective in the treatment of men with organic erectile dysfunction.[22] Although one of the trials of MUSE® involved a large group of patients, the dose was not selected by an open-label stepwise titration, as would be expected in clinical practice, and the study population was homogenous because all study sites were in the USA. Thus the conclusion from that study may not be applicable to a culturally diverse Malaysia.

Thus we conducted an open label study with MUSE®. This trial is conducted to confirm the efficacy and safety of transurethral alprostadil in multicultural eastern study population and to identify demographic factors that might influence the patients' response to therapy. The endpoints measured in this part of the study included erectile response on a five-point scale, sexual intercourse, patient comfort with the therapy, and adverse reactions.

2. AIMS OF THE STUDY

2.0 AIMS OF THE STUDY

2.1 To study the characteristics of patients with erectile dysfunction in Institut Urologi & Nefrologi (IUN), Hospital Kuala Lumpur (HKL).

2.2 To evaluate the safety and efficacy of transurethral alprostadil (MUSE®) in the treatment of patients with erectile dysfunction.

3. ANATOMY AND PHYSIOLOGY OF ERECTION

3.0 ANATOMY AND PHYSIOLOGY OF ERECTION

3.1 Anatomy of the penis

The penis can be described in term of structural component, vascular anatomy and neuroanatomy.

3.1.1 Structural component

The penis is a cylindrical organ consisting of: -

a) The base

b) The body and

The glans penis. (Figure 3.1)

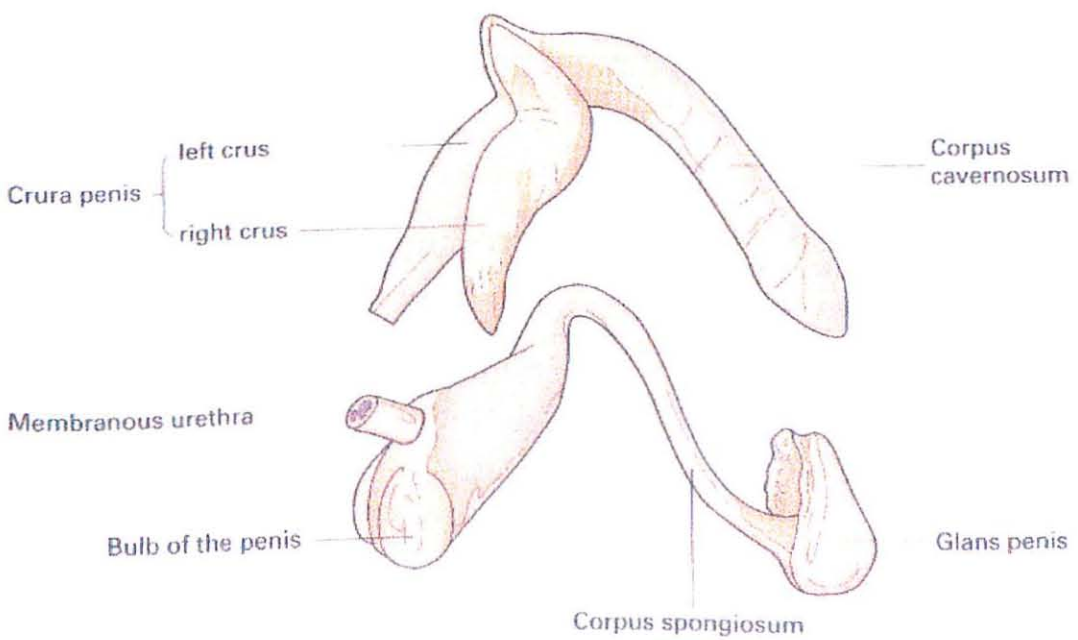

Figure 3.1 Structure of penis (adapted from Erectile Dysfunction. Current investigation and management by Ian Eardley and Krishna Sethia, 1998)

The base is attached to the bony pelvis and consists of the crura and the bulb. The paired crura are cylindrical structures attached to the ischial and the pubic rami. They meet in the midline where they become the corpora carvenosa. The ischiocavernous muscles cover them posteriorly. The bulb, which contains the urethra, pierces the urogenital diaphragm between the crura. It narrows anteriorly as the corpus spongiosum, where it comes to lie inferiorly or ventral to the corpora carvenosa and is covered by bulbocarvenous muscles. The body of penis is thus made up of three tubular structures, the paired corpora carvenosa and the inferiorly placed corpus spongiosum. Distally the corpus spongiosum is expanded to become the glans penis, within which the two corpora carvenosa terminate.

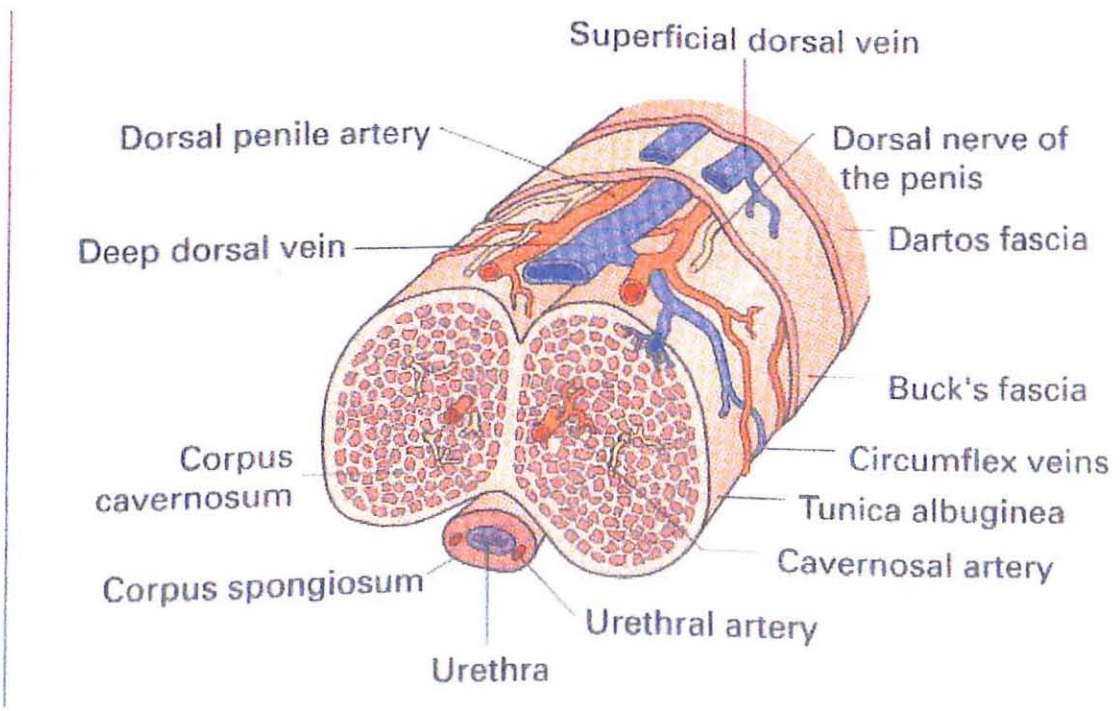

Figure 3.2 Cross-sectional anatomy of the penis (adapted from Erectile Dysfunction. Current investigation and management by Ian Eardley and Krishna Sethia, 1998)

The paired corpora carvenosa are surrounded by a dense fibrous sheath, the tunica albuginea. (Figure 3.2) The corpus spongiosum lies outside the tunica. The tunica albuginea is tough, fibrous and relatively indistensible. It is composed primarily of collagen and elastin, and traditionally is divided into two: an outer longitudinal layer, which surrounds both corpora, and an inner circular layer, which surrounds each individual corporal body. In the midline these two layers are fused and form a midline septum, which is incomplete distally. Inside the tunica lies the spongy tissue, which is essentially a vascular structure. Interconnecting sinusoidal spaces are surrounded by trabeculae containing smooth muscle cells which themselves lie in a stroma composed of collagen, elastin, blood vessels and nerves. The trabecular spaces are lined by endothelium and are fed by the helicine branches of the deep penile arteries. The corpus spongiosum has a similar anatomy although its tunica is much thinner (and is absent on the glans penis), while the sinusoidal spaces are larger.

On the dorsum of the penis are found the main neurovascular structures, namely the deep dorsal vein in the midline, flanked laterally by the dorsal penile arteries and the dorsal nerves of the penis. (Figure 3.2) These structures are enclosed by a condensation of the deep fascia, known as Buck's fascia, which is cylindrical prolongation of Colles' fascia. Superficial to this is the superficial dorsal vein of the penis, which lies within the loose superficial fascia which is itself covered by a rather thin, loose skin.

The penis is supported by two fascial ligaments. The fundiform ligament, which is a condensation of deep fascia, extends inferiorly from the linea alba and divides into two bands which enclosed the penis before meeting ventral to the shaft of the penis. Here they become confluent with the deep fascia of the scrotum. The suspensory ligament of

the penis is a short triangular ligament from the pubic symphysis to the deep fascia on the dorsum of the penis. It is this ligament that suspends the erect penis into a position perpendicular to the body, when a man is standing.

3.1.2 Vascular anatomy

Arterial supply of the penis

The arterial supply of the penis is from the internal iliac artery via the pudendal artery. (Figure 3.3) The latter leaves Alcock's fascial canal on the medial aspect of the obturator internus muscle and divides into the superficial perineal (scrotal) artery and continues as penile artery. It then pierces the urogenital diaphragm before dividing into its terminal branches, the dorsal penile artery, the cavernosal arteries (deep branch) and the bulbar artery. The bulbar artery supplies the bulb of the penis and the corpus spongiosum before passing to the glans. The cavernosal arteries provide most of the blood supply for the spongy tissue of the corpora carvenosa. The terminal branches are of two sorts: the coiled helicine arteries, which directly supply the sinusoidal spaces, and few smaller arterioles, which travel within the trabeculae. The helicine arteries are the main resistance vessels of the penis and control flow into the cavernosal sinusoids. When the penis is flaccid the main arterial flow is through the trabecular arteries and the helicine arteries are short, coiled and closed. During erection the blood is diverted into the helicine arteries, which elongate and dilate, thereby filling the sinusoidal spaces.

The dorsal penile arteries travel distally to the glans penis where they anastomose with the terminal branches of the artery to the bulb. As they pass distally they give off circumflex branches, which pass with the circumflex veins around the penis.

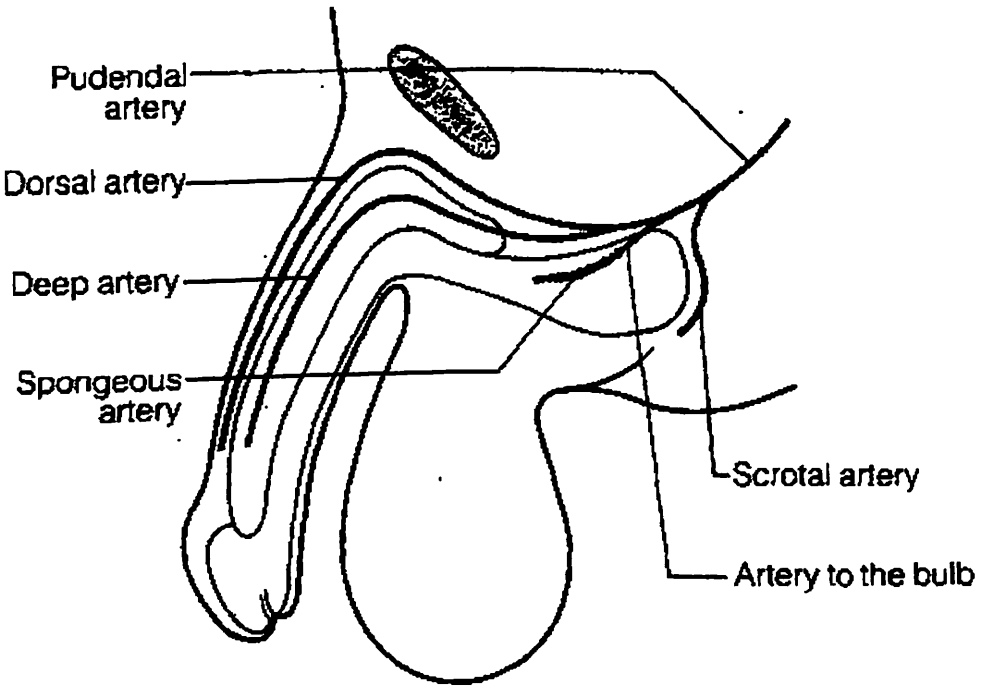

Figure 3.3. Arterial supply to the penis

There are often communication between the deep and the dorsal arterial systems, and occasionally a significant proportion of the cavernosal blood supply can be derived from the superficial penile arteries. It may be the circumflex arteries, which provide the structural basis for the communication. Occasionally there is an accessory arterial supply to the penis from obturator artery or even the external iliac artery.

Venous drainage of the penis

From the sinusoidal spaces, venous blood collects in a series of subtunical plexus, which lie beneath the tunica albuginea. These plexus drain via emissary veins, which pierce the tunica albuginea. (Figure 3.4) Distally, the emissary veins drain either into spongiosal veins or into circumflex veins, which in turn drain into the deep dorsal vein. Proximally, the emissary veins drain into the cavernous veins or crural veins, which then drain into the internal pudendal vein. (Figure 3.5)

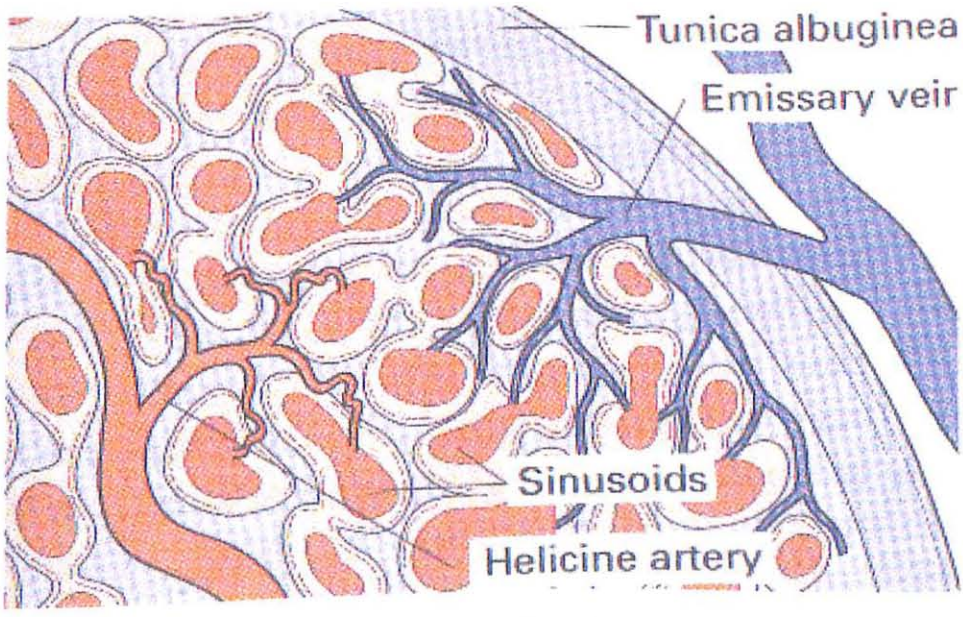

Figure 3.4 The cavernosal sinusoids (adapted from Erectile Dysfunction. Current investigation and management by Ian Eardley and Krishna Sethia, 1998)

The venous drainage of the glans penis is via a number of small veins which form a retrocoronal plexus from which the deep dorsal veins arises. The corpus spongiosum is drained by the spongiosal and bulbar veins into the deep dorsal vein. The deep dorsal vein travels proximally in the midline to pierce the suspensory ligament before passing

between the puboprostatic ligaments to enter the peri-prostatic venous plexus. The superficial dorsal venous complex drains the skin and the subcutaneous tissues of the penis and usually drains into the saphenous vein.

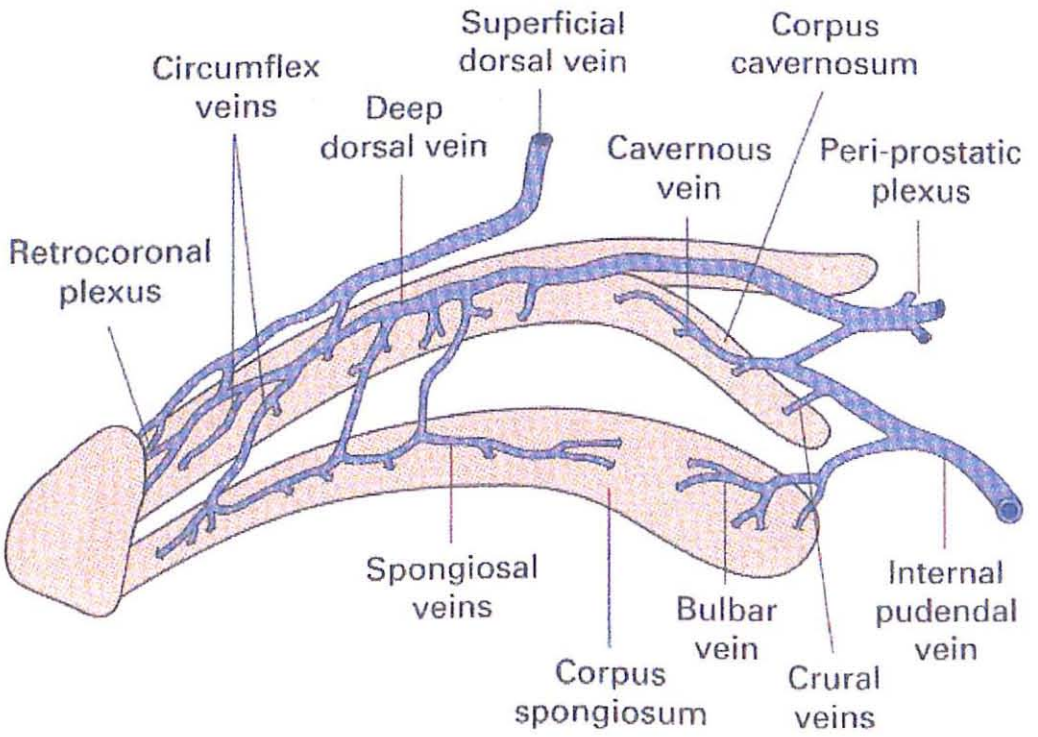

Figure 3.5 Venous drainage of the penis (adapted from Erectile Dysfunction. Current investigation and management by Ian Eardley and Krishna Sethia, 1998)

3.1.3 Nerve supply of the penis

The innervations of the penis are both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor). The parasympathetic innervation of the penis is the primary erectile innervation. It comes from the intermediolateral column of the sacral spinal cord and exits via the nerve root of S2, S3 and S4 to travel in the nervi erigentes

to the pelvic plexus, where some of them are joined by the sympathetic nerves from the superior hypogastric plexus.[25] Most fibers then synapse and post-synaptic fibers pass in the cavernous nerves to the penis. (Figure 3.6)

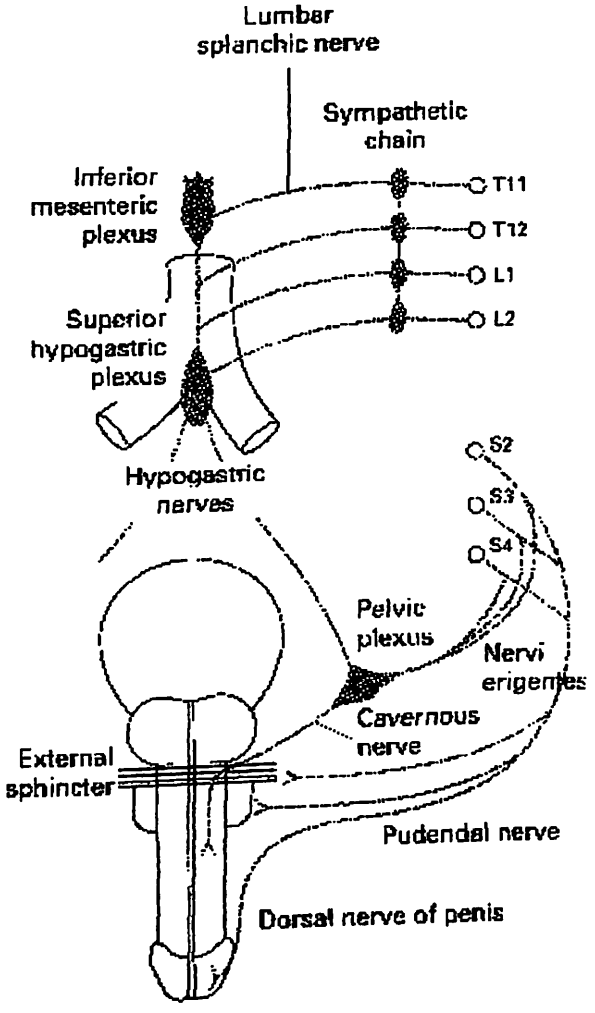

Figure 3.6. Nerves supply of the penis

Sympathetic nerves originate within the thoracolumbar cord (T11-L2) and then pass via ventral nerve roots and sympathetic chain to the hypogastric plexus before reaching the pelvic plexus.[13] Some fibers travel via lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexus. At this level there is considerable opportunity for integration with the parasympathetic innervation. Post-synaptic fibers then pass within the cavernous nerves to the penis. The cavernous nerve is important to surgeons, because of its relationship to the prostate, since it is at risk of damage during

open prostatectomy, radical excision of the rectum, or bladder. A clear understanding of these nerves is essential to prevent iatrogenic ED. Stimulation of the pelvic plexus and the cavernous nerves induce erection, whereas stimulation of the hypogastric nerve or sympathetic trunk causes detumescence.

The sensory innervation of the penis has a number of peculiar characteristics. For instance the glans penis has a receptor density that is higher than any other area of the body, with most nerves having free endings. The ratio of free nerve endings and the corpuscular receptors are 10:1. Physiologically the receptors of the glans have a high tactile threshold and a low pain threshold, compared with glabrous skin, which has the opposite characteristics. Afferent information is carried mainly via Aδ and C fibers within the dorsal nerve of the penis and pudendal nerve, spinal cord and spinothalamic tract to the thalamus and sensory cortex for sensory perception. Efferent fibers are also present in the pudendal nerve, and provide the motor supply for the ischiocavernosus and bulbocavernosus muscles.

3.2 Hemodynamic and mechanism of erection and detumescence

3.2.1 Corpora Cavernosa

The penile erectile tissue, specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. In the flaccid state, these muscles are tonically contracted under influenced by the sympathetic discharge, which is more predominant, and vasoconstrictors secreted

by endothelium allowing only a small amount of arterial flow for nutritional purposes (1.4 to 4.0 ml per minute per 100gm of tissue).

Psychic stimuli (received or generated in the brain) or physical stimuli of the genital organ causes transmission of nerve impulses from the spinal cord to the cavernous nerves (via autonomic nervous system) thereby releasing neurotransmitter.[1] This results in relaxation of these smooth muscles and the following events where by Lue *et al* in San Francisco identified 8 separate phases of erection [56].

Phase 0: The flaccid phase

The penis is flaccid under predominantly sympathetic neural tone. The arterial inflow is low (typically less than 15cm/sec) and the trabecular smooth muscle is contracted. Blood gases are similar to venous blood. (Figure 3.4)

Phase 1: The filling phase

Parasympathetic stimulation leads to arteriolar dilatation with a massive increase in arterial flow to greater than 30cm/sec. Sinusoids filled without any significant increase in intracavernosal pressure.

Phase 2: The tumescent phase

The intracavernous pressure rises leading to relative fall in the arterial inflow. As pressure increases above diastolic blood pressure, flow continues only during the systolic phase. As the sinusoids expand there is some compression of the subtunical venous plexus. (Figure 3.7) The penis elongates and expands to its maximal capacity

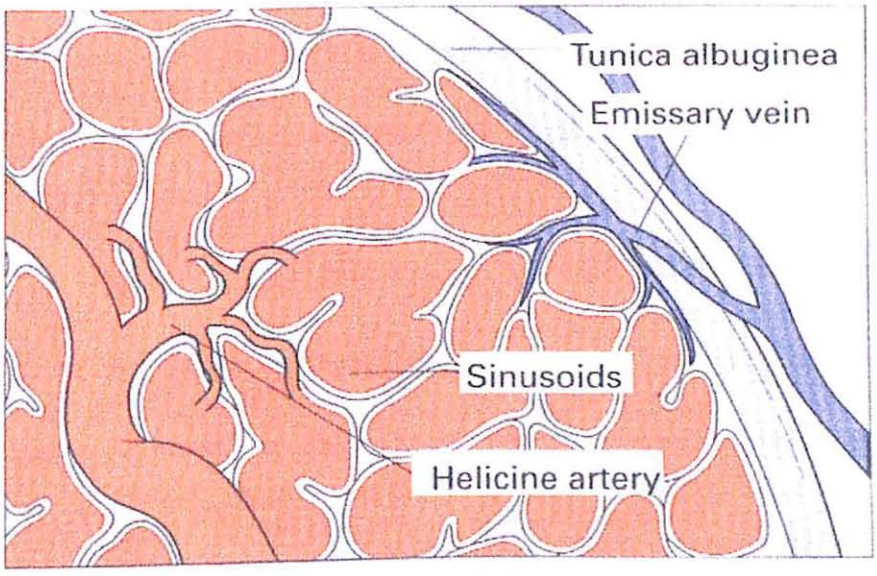

Figure 3.7 The cavernosal sinusoids during erection (adapted from Erectile Dysfunction. Current investigation and management by Ian Eardley and Krishna Sethia, 1998

Phase 3: The full erection phase

The intracavernosal pressure rises to around 90% of systolic pressure. The arterial flow to the penis falls but still greater than in flaccid state. The sinusoid expanding and compressed the emissary veins. The blood gases are similar to the arterial blood.

Phase 4: The rigid erection phase

The ischiocavernosus muscles contracts and thus squeezing the crura and causes the intracavernous pressure to rise above the systolic pressure. The ischiocavernosus muscle can contract voluntarily or under the bulbocavernous reflex. The arterial inflow will cease and the emissary veins will be completely compressed and closed thereby forming the penis as a close space. This is called the 'veno-occlusive mechanism'.

Phase 5: The initial detumescence phase

There is a small transient increase in the intracavernosal pressure, probably due to sympathetic stimulation against a closed venous outflow.

Phase 6: The slow detumescence phase

There is contraction of the trabecular smooth muscle and constriction of the helicine arterioles with a fall in the intracavernosal pressure leading to reduced compression of the subtunical veins and increased venous outflow.

Phase 7: The fast detumescence phase

Under the sympathetic stimulation, there is a fall in both arterial inflow and intracavernosal pressure, with an increase in venous outflow and rapid detumescence.

3.2.2 Corpus Spongiosum and Glans Penis

The Hemodynamic of the corpus spongiosum and glans penis are somewhat different from those of the corpora cavernosa. During erection, the arterial flow increases in a similar manner; however, the pressure in the corpus spongiosum and glans is only one-third to one-half that in the corpora cavernosa because the tunical covering (thin over the corpus spongiosum and virtually absent over the glans) ensures minimal venous occlusion.

3.3 Smooth Muscle Physiology

Spontaneous contractile activity of cavernous smooth muscle has been recorded in vitro and in vivo studies, where they found two types of electrical activity recorded from the corpus cavernosum, i.e. spontaneous and activity-induced. Field stimulation results in a decrease in tension and intracellular calcium at low frequencies and an increase in tension and intracellular calcium at high frequencies. In general, the response to pharmacological agents correlates with the change in intracellular calcium.

As described above, the cerebral impulses normally travel through sympathetic (inhibiting norepinephrine release), parasympathetic (releasing nitric oxide and acetylcholine), and somatic (releasing acetylcholine) pathways to produce a normal rigid erection. In patients with a sacral cord lesion, the cerebral impulse can still travel via the sympathetic pathway to inhibit norepinephrine release, and nitric oxide and acetylcholine can still be released via synapse with postganglionic parasympathetic and somatic neurons. Because the number of synapses between the thoracolumbar outflow and postganglionic parasympathetic and somatic neurons is less than the sacral outflow, the resulting erection will not be as strong.

In men, there are three distinct types of erection present, namely psychogenic, reflexogenic and nocturnal. Psychogenic erection is a result of audiovisual stimuli or fantasy. Impulses from the brain modulate the spinal erection centers (T11-L2 and S2-S4) to activate the erectile process. The mechanisms are thought to involve both the sympathetic and parasympathetic pathways. These erections can occur in men with complete lesions in the lumbar cord and cauda equina while sympathectomy also does

not lead to loss of these erections. It is common in younger men, but decrease gradually with increasing age.[56]

Reflexogenic erection is produced by tactile stimuli to the genital organs. This response is abolished by damage to the sacral spinal segments, the spinal nerve roots, the pelvic nerves, the pudendal nerve and the cavernous nerve. All these findings suggest the presence of a sacral spinal reflex with afferent fibers carried in the dorsal nerve of the penis and the pudendal nerve, with the efferent fibers carried within the sacral parasympathetic fibers. The impulses reach the spinal erection centers; some then follow the ascending tract, resulting in sensory perception, while others activate the autonomic nuclei to send messages via the cavernous nerves to the penis to induce erection. This type of erection can present in men with high spinal cord injury. For example, in men with complete thoracic lesions, reflex erections can be elicited by manual stimulation of the penis. In men with lesions below this, reflex erections appear much less frequently. It is assumed that thoracic lesions are associated with a complete loss of descending impulses from higher centers, while in men with lower lesions, there may be ischaemic damage to the sacral segments of cord, which lead to abolition of the reflex.[13]

Nocturnal erection occurs mostly during rapid-eye-movement (REM) sleep and it is usual for a potent man to have between four to six erections per night. The mechanism is as yet unknown. However, it is generally assumed that the presence of normal nocturnal erections indicates a diagnosis of psychogenic impotence; this need not be true if the pathways, which mediate the two types of erections, are different.[15, 56]

3.4 Neurotransmitters

3.4.1 Peripheral Neurotransmitters

The process of erection is generally accepted to be under neuroregulatory control and involves the cholinergic, adrenergic and nonadrenergic noncholinergic neuroeffector systems. However, biochemical substances locally released from the endothelial or smooth muscle components of the erectile tissue may also cooperate in this function.

Adrenergic nerve fibers and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter to control penile flaccidity and detumescence. Receptor binding studies have shown the number of α-adrenoceptors to be 10 times higher than the number of ß-adrenoceptors.[56]

Mediators that have been proposed to function as nonadrenergic noncholinergic neurotransmitter include:

1. Neuropeptides such as vasoactive intestinal peptides, calcitonin gene-related peptide and substance P.
2. Purines example adenosine, adenosine triphosphate.
3. Other factors include decarboxylated amino acid, histamine, serotonin, prostaglandin and bradykinin.

Acetylcholine is required for ganglionic transmission (by nicotinic receptors) and vascular smooth muscle relaxation (by muscarinic receptors). Cholinergic nerves have

been demonstrated within the human cavernous smooth muscle and surrounding penile arteries, and ultra structural examination has also identified terminals containing cholinergic vesicles in the same area. It has been suggested that acetylcholine stimulates the release of nitric oxide (NO) from endothelial cells and thus contributes directly to smooth muscle relaxation during erection.[8]

Latest development also found that NO as the elusive agent of penile erection. It was first described in 1979 as a potent relaxant of peripheral vascular smooth muscle, with an action mediated by cGMP. Subsequently, endothelium-derived relaxing factor was identified as NO or chemically unstable nitroso precursor. [14] Nitric oxide is synthesized from endogenous L-arginine by NO synthase (NOS) located in the vascular endothelium. Nitric oxide may be synthesized and released as a neurotransmitter by the nonadrenergic /noncholinergic (NANC) neurons after their excitation by either electrical or chemical stimulation. A primary biochemical role for nitric oxide is to stimulate the increased intracellular production of the second messenger molecule, 3', 5'-cyclic guanosine monophosphate (cGMP). [8, 54] Recent observations strongly suggest that NO released from NANC neurons increases the production of cyclic guanosine monophosphate (cGMP), which in turn relaxes the cavernous smooth muscle via biochemical cascade. It has also shown that the NO-mediated responses are progressively inhibited as a function of decreasing oxygen tension; reverting to normal oxygen tension restores endothelium-dependent and neurogenic relaxation. Currently, NO or a NO-like substance appears to be the most likely principal neurotransmitter causing penile erection. In this regard Ignarro *et al* have suggested that NO is highly labile; therefore, it cannot be stored as a preformed neurotransmitter. There are at least three distinct forms of NOS (neuronal, endothelial and macrophage).[8, 56]

Other investigators believe that VIP may be one of the neurotransmitters responsible for erection. VIP-immunoreactive nerve fibers have been identified within the cavernous trabeculae and surrounding penile arteries, and neurostimulation-induced cavernous smooth muscle relaxation has been shown to be blocked by a VIP antagonist or anti-VIP serum. Other potential candidates include calcitonin-gene-related peptide (CGRP) peptide histidine methionine, pituitary adenylate cyclase-activating polypeptide 32, and prostaglandin 33,34. Prostaglandin E1 receptor density is reported to be lower in impotent men. Although these neurotransmitters may participate in the erectile process, their exact role is still unclear.[1, 56] Nevertheless, because of the multiplicity of putative transmitters present in the corpus cavernosum and in perivascular nerves, further investigation is needed to elucidate the interactions between neurotransmitters and neuromodulators at the neuromuscular junction, and between the neural and endothelial control of vascular tone.

3.4.2 Central Neurotransmitters

In animals, the hypothalamus is known to have central role in the erectile activity. Other important areas include the medial preoptic nucleus (MPON) and the paraventricular nucleus (PVN). From these nuclei there are a number of descending tracts, which project into the spinal nuclei which innnervate the penis. A variety of neurotransmitters are involved in these pathways namely catecholamines, 5-hydroxytryptamine (5-HT), γ-amino-butyric acid (GABA), oxytocin, prolactin, melanocyte stimulating hormone (MSH), adrenocorticotrophin (ACTH) and opioid neurotransmitter. In man, there are evidence that dopamine, norepinephrine, prolactin,

MSH and 5-HT do have a role in penile erectile activity.[56] It is suggested that dopaminergic and adrenergic receptors may promote sexual drive, and that serotonin receptors inhibit it. However, most of this evidence derived either from the animals studies or from the use of pharmaceutical agents in men with or without erectile dysfunction.

4. AETIOLOGY OF ERECTILE DYSFUNCTION

4.0 AETIOLOGY OF ERECTILE DYSFUNCTION

Erectile dysfunction is a complex multifactorial syndrome, often involving both psychological and physiological factors (organic factors). About 20 to 30 years ago, the main cause of erectile dysfunction was believed to be psychogenic in origin.[3, 21] However, in 1970s and 1980s, experts believed that erectile dysfunction always had an organic cause. Now, it is accepted that erectile dysfunction is commonly due to a complex interaction between psychological and physical problem. In any one person, there may be a number of different mechanisms active at one time. In younger patient, it is likely that psychological cause predominates. While in men aged over 50, the organic causes are more common. To date, organic ED has been most frequently attributed to vascular abnormality (arteriogenic) and/or cavernosal (venogenic or venous incompetence) as well as neurogenic abnormalities.[1, 3] In these cases, 50-70% result from a combination of arterial insufficiency and venous incompetence, 30% due to arterial insufficiency alone and in 15% as a result of veno-occlusive dysfunction.

However, other causes of organic ED are currently widely recognized including endocrine in origin and drug-induced. Many classifications have been proposed for ED. Some are based on the causes such as diabetic, traumatic, prostatic carcinoma etc, while others are based on neurovascular mechanism of erectile process itself such as neurogenic, arteriogenic or venogenic. There was a new classification of ED suggested by D. Udelson *et al* (1998) that based on factors which determine erectile rigidity such as intracavernosal pressure, penile tissue mechanical property characteristics and penile geometry.[11] Here are some of the causes of ED.

4.1 Arteriogenic causes of erectile dysfunction

Arterial disease can cause ED by restricting the inflow of blood to the penis. Atherosclerotic or traumatic arterial occlusive disease can reduce the perfusion pressure and arterial flow to the sinusoidal space and thus increasing the time needed to attain maximal erection and reducing the rigidity. It is also suggested that the atheroma leads to poor blood flow, which in turn causes relative ischaemia and impaired cavernosal oxygenation. This leads to smooth muscle dysfunction with associated veno-occlusive dysfunction. [56] Ischaemia ultimately results in loss of cavernosal smooth muscle with increasing fibrosis. There is also evidence that ischaemia can lead to changes in the structure of the tunica albuginea with alteration in the elastin and collagen content. These changes in structure may lead to changes in the function and efficacy of veno-occlusive mechanism. [18, 56]

Atherosclerotic disease is the cause of approximately 40% of ED in the men older than 50 years.[3] The cardiovascular disease can affect potency by variety of mechanism. ED occurs in up to 45% of patients post myocardial infarction. However, psychological factors also play an important role in these cases because some may not dare to exert himself in doing sexual intercourse. The incidence and age of onset of coronary disease and ED are parallel suggesting common risk factors such as hypertension, hyperlipidaemia, cigarette smoking and diabetes mellitus as the cause for generalized arteriosclerosis. Hypercholesterolemia that destroys the endothelium reduces relaxation of the smooth muscle cells which predisposing to ED. On the other hand, smoking can abolished venous restriction ability in animal's study.[18] It is also well known that hypertension is associated with erectile dysfunction. But it is difficult to dissociate from