# ERECTILE DYSFUNCTION: CURRENT STATUS

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The association between diabetes and erectile dysfunction (ED) was first noted in 1798, but has become a well recognised entity only in the last three decades [1,2]. It is estimated that between 23-69% of diabetic patients will have some erectile dysfunction [3,4]. It is also noted that in diabetics of less than 5 year duration, no dysfunction is noted and after 15 years of diabetes, more than 50% will have mild to severe variety of E.D. [4].

The cause of E.D. is unclear, but could be due to neurogenic, vasculogenic or mixed variety. Ellenberg et al [2] have suggested autonomic neuropathy as the chief cause. Phermal et al [5] in 1972, were the first scientist to report histological evidence of neuropathy after cavernosal biopsy. Melman et al [6] have claimed E.D. to be due to a reduction of norepinehrine levels. Jevitch et al [7] have reported an obstructive vasculogenic etiology. Thus, till today, the exact cause and frequency of erectile dysfunction is far from clear.

## ANATOMY AND PHYSIOLOGY

### The Arterial Supply:

Internal pudendal artery and its anterior division, after passing through alcock canal, divides into 4 branches. The most important is deep dorsal artery which enters cavernosal tissue at its base and branches sequentially, ultimately ending as 'Helicine artery'. This is surrounded by sinusoids. The erection is a process which is neurologically mediated, resulting in vasculogenic engorgement thus giving tumescence, rigidity of penis. There are standard 6 phases which goes in a serial manner, intial filling, tumescence, full erection, rigid erection and detumescence [8].

The flaccid state is adrenogenic while the vascular phase is non andrenogenic. Once the ejaculation occurs, the blood drains out of sinusoidal, emissary veins which are completely blocked at the height of erection. This constitutes as important phase of venoocculusive mechanism [8].

The venous blood later is drained by crural, deep dorsal veins into preprostatic plexus, thus bringing detumescence [8].

### Neurophysiology

The smooth muscles of the cavernous trabeculate and the arterioles control tumescence and detumescence of the penis. The regulation of erection is probably controlled by impulses from both the sympathetic and parasymathetic nervous systems and the local factors released from the endothelium.

### Central Neurotransmitters

The medial dorsal nucleus of the thalamus and the medial preoptic area (MPOA) control penile erection and sexual drive. Enhancement of sexual drive is accomplished through the action of dopaminergic and adrenergic receptors and inhibited by serotonergic receptors.

### Peripheral Neurotransmitters

The principal transmitter for erection is nitric oxide which can be released from nerve endings or endothelial cells. Other candidates include: Acetylcholine and vasoactive intestinal polypeptide (VIP). The candidates for detumescence include norepinephrine, endothelin and neuropeptide Y [9].

### Peripheral Neuroanatomy

Parasympathetic fibers of the erection originate from S 2-4 while the sympathetic fibers originate from T10-12. These fibers join together to form pelvic plexus. The cavernous nerves course posterolateral to the prostate. The medial bundle is close to the membranous urethra and enters the penis in the hilar area. The lateral bundle penetrates the GU diaphragm to innervate the crura. Some of the fibers join the dorsal nerve and use it as a carrier to innervate distal portions of the penis.

### Hemodynamics of an erection

Erection is neuro-vascular phenomenon under psychologic control. It involves increase arterial flow, increased venous resistance and relaxation of sinusoidal spaces. There are 2 components in penile erection: Vascular component controlled by the autonomic nerves and muscular component by the somatic nerves.

In the flaccid phase there is minimal inflow and outflow.

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Penile erection and detumescence consists of 7 phases:

I. Initial filling phase-maximal inflow with no increase of intercavernous pressures;

II. Tumescence phase-Increasing intracavernous pressure with decreasing arterial flow;

III. Full erection phase-Intracavernous pressure reaches a plateau which is slightly below the systolic arterial pressure, small inflow and outflow;

IV. Rigid erection phase-Intracavernous pressure temporarily jumps to well above systolic arterial pressure due to contraction of the ischiocavernous muscles, temporary shut down of inflow and outflow;

V. Initial detumescence phase-Transient increase of intracavernous pressure due to smooth muscle contraction against a closed venous system;

VI. Slow detumescence phase-Slow decrease of intracavernous pressure from slowly opening venous channels;

VII. Fast detumescence phase-Fast decrease of intracavernous pressure to base line from completely re-opened sinusoids-venous drainage.

## CLASSIFICATION OF IMPOTENCE

According to the factors involved, impotence can be classified as follows :-

1. Psychogenic – mind, anxiety and stress
2. Neurogenic – brain, spinal cord, pelvic and cavernous nerves, neurotransmitters.
3. Hormonal – hypothalamic – pituitary – testicular axis, thyroid, adrenal
4. Arterial – heart, aorta, hypogastric, pudendal, penile artery and its branches.
5. Cavernosal – tunica albuginea, cavernosal smooth muscle, gap junctions, endothelium, emissary veins.
6. Drug-Induced-legal and illegal drugs [11].

## PHYSIO-PHARMCOLOGY

Penile erection is a haemodynamic process involving relaxation of smooth muscle of the corpus cavernosum and its associated arterioles.

This relaxation process results in an increased flow of blood into the trabecular spaces of the corpora cavernosa. Smooth muscle relaxation is mediated by nitric oxide (NO) which during sexual stimulation is synthesized in the nerve terminals of parasympathetic non-andrenergic, non-chlolinergic (NANC) neurons in the penis and by the endothelial cells lining blood vessels and the lacunar spaces of corpus cavernosa.

The NO activates guanylate cyclase resulting in an increased conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP provides the signal which leads to relaxation of smooth muscle of the corpus cavernosum and penile arterioles. The level of cGMP is regulated by a balance between the rate of synthesis by guanylate cyclase and the rate of hydrolytic breakdown to guanosine 5’ – monophosphate (GMP) by cyclic nucleotide phosphodiesterase (PDE) isozymes.

1. Therefore, agents that inhibit cGMP hydrolysis may increase the cGMP signal and could be expected to enhance relaxation of smooth muscle in the corpus cavernosum and thereby facilitates penile erectile responses.

   Of the PDE isozymes, PDE 5 and PDE 6 are monospecific for cGMP as a substrate. PDE 3 and PDE 4 preferentially hydrolyses cyclic adenosine monophosphate (cAMPO) and PDE 1 and PDE 2 to accept both cGMP and cAMP as substrates.

2. We have shown that the major PDE activity in Human Corpus cavernosal tissue is cGMP specific PDE5 with lower level of PDE 2 and PDE 3 also present.

3. Sildenafil is a potent inhibitor of the cGMP specific PDE5 isolated from human corpus cavernosum (HCC). It effectively blocks PDE 5 mediated hydrolysis of cGMP and has an IC50 of 3.9 nM3-Slidenafil has low potency against PDE2 and PDE3, the other phosphodiesterases found in HCC and is also a weak inhibitor of PDE 4 (IC 50 Values 7300 nM). It has moderate activity against PDE 1 from human cardiac ventricle (IC 50 290 nM) and inhibits PDE 6 activity isolated from bovine retina with a mean IC 50 of 33nM, i.e. 9-fold higher than that for inhibition of PDE 5.

Electrical field stimulation (EFS) of the tissue samples caused transient frequency dependent relaxation responses that were shown to be mediated by neuronal NO acting via stimulation of guanylate cyclase.

There is now considerable evidence that NO, acting via cGMP is the main physiological mediator of penile erection. The results of in vitro and clinical studies with sildenafil summarised here, are consistent with the proposal that PDE 5 is the main regulator of cGMP levels during penile erection, and therefore selective inhibitors of PDE 5 can enhance the erectile process[9].

## Summary of Physio-pharmacology of Penile erection

a) The neurotransmitters of the sympathetic (anti-erectile) and parasympathetic (erectile) nerves contribute to contraction and relaxation respectively of C C muscle. The motor neruo-transmitter is adrenergic acting on alpha adrenoceptors and the inhibitory neurotransmitter (which is nonadrenergic, non-cholinergic) is nitrenergic, (i.e. the mediator being NO releasing cGMP for the relaxation).

b) The modulators of the above neurotransmitters, especially the inhibitory modulation (e.g. PGE and VIP), on persistent adrenergic neurotransmission to unmask the nitrenergic neuro-transmission.

c) Endogenous release of autocoids acting approximately on their respective contractlie receptors (for detumescence) or relaxant receptors (for tumescence). Relaxant responses of some of these autocoids are via cAMP.

Following the relaxation of the C C muscle and dilation of the arterial bed in the penis the haemodynamic aspects of the erectile process involve the flow of blood into the erectile tissue initiating engorgement. As the engorgement of the penis progresses to the maximum, the blood loss from the penis (i.e. the venous drainage), becomes minimal due to the increased pressure in the chamber of the C C muscle exerted against subtunical venules and emissary veins. Since the tunica albugnea surrounding the C C chamber has limited expansion, this process causes further engorgement, erection and rigidity (Fournier et al, 1986, Kano et al, 1987) [9,10]

## HISTORY AND PHYSICAL EXAMINATION

Cardinal features differentiate organic from psychogenic impotency: 1. time, 2. presence of ejaculation 3. situational impotency 4.loss of libido.

In drug history, hormonal injections, antihypertensive, antipsychotic and antidepressant drug history must be asked.

Street drugs, alcohol and smoking must be asked. Detailed history of various operations in pelvis, rectum and bladder are also asked. CRF, diabetes, liver failure, hypo-hyperthyroid and multiple endocrinopathy history must be looked for. In short detail of sexual history, initiation, maintenance and ejaculation is necessary. History of trauma and cycle rides should be necessary. Cigarette, street drugs, hypertension, hyperlipidemia are important. In failure to store (venous), smoking and trauma are important history.

Physical examination includes secondary sexual characteristics and mental disposition. The frenulum and fore skin tightness is noted. The plaque, calcification on dorsal of penis is noted.

The size, position and number of testis are noted. Rectal examination, BCR, perineal sensation and distal neuro-vascular examination are of paramount importance. Breast and upper extremity examination completes the physical examination.

## DIAGNOSTIC TESTS

*Nocturnal Penile Tumescence (NPT) Test:* The first widely used test was NPT test. Karacan et, 1975. NPT testing is based on the finding that a normal man has two or four episodes of erection at night usually in association with REM sleep. Men with psychological impotence continue to have these nocturnal erections, while men with organic impotence show impairment or absence of these erections. Thus, NPT monitoring provides an objective test for distinguishing between organic and psychogenic impotence.

The widespread use of this test in the 1970s led investigators to realise that an unexpectedly large proportion of cases of erectile dysfunction were due to organic causes. This realization, in turn, provided an incentive to the development of a large number of investigative procedures and basic physiologic studies. Today, our understanding of the erectile process and its disturbance has reached a great level of refinement, allowing for precise diagnosis.

*Pharmaco diagnostic testing with Intracavernosal injection of vasoactive drugs (ICIVAD).*

This simple office test has revolutionised the investigation of impotence. It consists of the injection of vasodilator drugs like papaverine, phentolamine mixture and prostoglandin E1 into penis. This caused dilation of the penile cavernosal arteries and relaxation of the cavernosal smooth muscle (which activates the venoocclusive mechanism), thus, producing an erection. Normal men will respond with a full and sustained erection. Hence, failure to achieve an adequate erection after ICIVAD with maximum dose implies a significant vascular problem, while attainment of a full erection, especially at a lower dose would indicate that the vascular mechanisms are normal. This, however, is not strictly true. Some men with pure psychogenic impotence and marked anxiety will have only a partial response, especially if only papaverine is used. On the other hand, some men with mild to moderate vasculogenic insufficiency can attain a near full erection when coupled with a combination of drugs. Thus the outcome of a diagnostic ICIVAD test can vary with the drug used.

In our experience, a papaverine-phentolamine mixture or pure PGE 1 by far gives the most useful results. Pure papaverine is not reliable in identifying vascular insufficiency since it will produce many false negative responses (poor erections in normal men)[13]. During ICIVAD it is important to provide adequate privacy, visual sexual stimulation and tactile penile stimulation (by self stroking or a vibrator). Only then will the best potential erection be evoked. Failure to use these measures will result in a false abnormal response.

## Penile Duplex Ultrasound Study

The use of a duplex ultrasound allows simultaneous ultrasonic visualisation of the penile structure and Doppler measurement of arterial blood flow. The sonographic mode is used to scan the corporator fibrosis and calcification. These would indicate cavernosal damage which, if severe, would contraindicate any attempt at revascularization. The cavernosal arteries are studied for thickening or calcification of the vessel wall and for changes in vessel diameter after ICIVAD. Minimally dilating (diameter 0.5 mm). Thick walled vessels would indicate penil arterial involvement as the cause of impotence. The Doppler mode gives information on the arterial wave-form and provides measurement of the peak systolic velocity (PSV) and the end diastolic velocity (EDV)[10].

The Resistance Index (RI) can be calculated from these parameters (RI=1-EDV=PSV). An abnormally slow (25 cm/sec) or equivocal result indicates arterial insufficiency. Persistent and diastolic flow (5 cm/sec) and flow RI indicates venous leak.

## Other Tests

Cavernosometry and graphy are necessary to confirm venous leak. These tests are invasive and are indicated only when surgery is being contemplated. With venous ligation surgery falling out of vogue, these studies are performed only infrequently.

*Penile angiography:* An invasive test which is done if only revascularization procedure is contemplated.

*Neurological Test:* The simplest is a biothesiometry, which is a modified tuning fork, whose frequency is fixed and amplitude variable. The body points are compared. This is a good screening test.

*Hormonal Assay:* Only indicated in hypoganadotropic hypogonadism and signs of visual disturbance along with headache. The GTT and glycosylated haemoglobin is far more important.

*Drug History:* Antihypertensive, antipsychotics and antidepressant are commonest. Street drugs usage is ever increasing. Cigarette and alcohol are also important factors.

## INVESTIGATING IMPOTENCE: A PRACTICAL APPROACH

In 90% of cases, an accurate working diagnosis can be reached through the use of ICIVAD (intra cavernosal injection of vasco active drugs) in combination with proper history [14,15].

Other simple office tests like penile doppler study, penobrachial index, biothesiometry etc. provide additional information but do not affect the management protocol.

More sophisticated tests like Rigiscan NPTR monitoring, (Fig. 1-3) duplex colour doppler

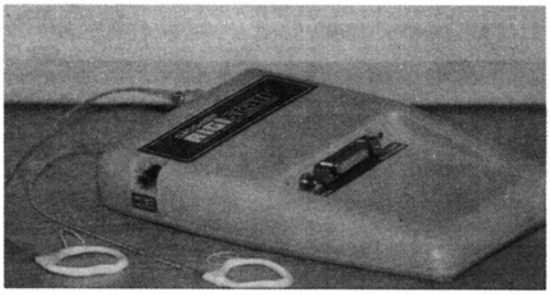

Fig. 1: Regiscan (NPT Device)

studies, Pharmaco-cavernosometry and graphy etc. are required only in equivocal cases or when surgery is being considered.

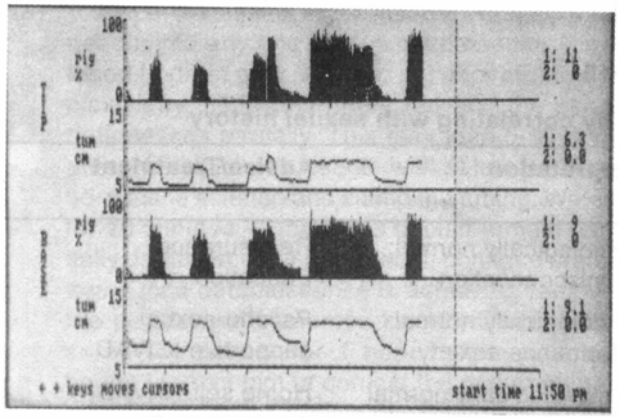

Fig. 2: Normal NPT – (Regiscan)

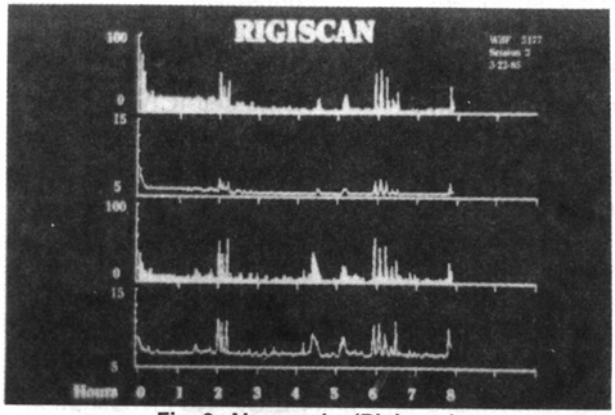

Fig. 3: Abnormal – (Rigiscan)

**ICIVAD-TEST PROCEDURE (Fig. 4)**

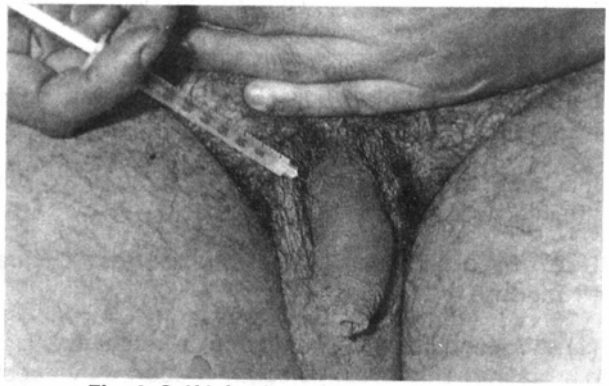
Fig. 4: Self Injection of Prostaglandin E1

1) Test should be carried out in a quiet room with assured privacy.

2) Extent of pre-explanation and taking of signed consent prior to ICIVAD are a matter of individual choice.

3) With one hand the penis is stretched to expose the shaft of the penis.

4) The skin is cleaned with spirit.

5) An insulin syringe with a ½ inch 27 G or 28 G is used for the injection. The needle is introduced perpendicular to the shaft at 2 O'Clock or 10 O'Clock positions (into any one corpus cavernosum), avoiding visible, superficial veins. The needle is pushed up to the hub.

6) The medicine is injected slowly. If resistance is felt, the angle of injection is changed.

7) The needle is withdrawn and the penis is massaged gently for 15 seconds.

8) The patient is then left alone and is instructed to stroke the penis gently and fantasize sexually (audio-visual aids may be used). This step is very important to ensure a true response.

9) The response is assessed every 5 minutes for 30 minutes. The patient is asked to compare the resulting erection with his morning and sexual erections and to opine whether he feels the erection is adequate for intercourse.

10) If the response is poor, a higher dose may be injected after 30 minutes or at the next session.

If the response is good, *the patient must not leave the clinic till he detumenscences.* Observe the patient every 30 minutes for 3 hours. Distinguish between these responses by carefully inquiring about the occurrence of erections at night, in the morning (with a full bladder) and during masturbation – the occasional presence of a full, sustained erection would confirm the diagnosis of a psychogenic problem. This may be further correlated with the age of the patient and the presence or absence of vascular risk factors.

In the older men, this distinction is not important since the treatment, in either case would be consist of home self ICIVAD. In younger men, an NTPR test may be required to establish the diagnosis and reassure the patient.

A partial erection after full dose in a young patient usually indicates a moderate vascular problem but must be confirmed by NPTR and ICI of trimix before proceeding with surgery.

A partial erection after full dose in an older patient usually indicates a moderate vascular problem. If this correlates with presence of vascular risk factors and history of diminished morning/masturbatory

erections, then it would suffice to test with trimix and consider surgery or VED if the response is poor.

If there is minimal erection (tumescence only), after full dose, and this correlates with the history, then a diagnosis of severe vasculogenic impotence can be made. Further investigations would be required only as appropriate to the further therapy to be offered. (Table 1).

**Table 1**
**Interpretation of diagnostic ICIVAD by correlating with sexual history**

| Response to ICIVAD | Natural Erection reported as | Interpretation | Advice / Treatment |
|---|---|---|---|
| 1. Full | Sexual: Full<br>Morning: Full | Physiologically normal; | Reassurance/ Education |
| 2. Full | Sexual: Not full | Physiologically normal; performance anxiety. | Psycho-sexual Supportive ICIVAD. |
| 3. Full | Sexual: Not full<br>Morning : Not full | i.Physiologically normal; with severe anxiety. II. Mild vasculogenic NPTR may be required to differentiate i. And ii. | Home self-ICIVAD, sex therapy & counselling |
| 4. Full | Sexual: Poor | Neurogenic problems. | Home self-ICIVAD; Penile Prosthesis, V.E.D. |
| 5. Partial Short-lived | Sexual : Partial<br>Morning: Partial | Vasculogenic problems | V.E.D – No investigation needed. Prosthesis-NPTR to confirm diagnosis, vascular surgery – NPTR & vascular studies. |
| 6. Poor | Sexual : Poor<br>Morning: Poor | Severe Vasculogenic | V.E.D – No investigation needed. Prosthesis – NPTR optional |
| 7. Partial | Sexual : Better<br>Morning: Better | Inadequate | Repeat with higher dose. |

If the test response is reported as poorer than the natural erections experienced by the patient, the test must be considered inadequate and repeated on another occasion with a higher dose.

Thus by comparing the ICIVAD – induced erection with the best sexual and morning erections experienced by the patient it is usually possible to reach a useful working diagnosis without the need for further testing as is summarized below and note the time to partial detumescence. This will help decide by how much to reduce the dose the next time. If penis is still fully erect at the end of 3 hours, injection of adrenaline should be give (see below). If the penis does not detumescence within 10 minutes of injecting adrenaline insert a 21 G scalp

vein needle and allow external drainage till the penis detumesces partially; then re-inject adrenaline. Reduce the dose by 50% to 70% at the next session.

It is inadvisable to send the patient home to "try out the injection" at the very first session.

### Use of Adrenaline for Detumescence: Office Procedure

1) Working solution: 1 ml (1 mg) adrenaline + 9 ml saline. This is conveniently prepared by directly aspiration into a 10ml syringe.

2) Using a 27 G needle, inject 0.25 ml (0.025 mg) to 1.0 ml (0.10 mg) of the dilute adrenaline solution into the penis and wait for 10 minutes. The higher dose is used in young men, while the lower dose is safer in older men. In men with IHD or arrhythimas or hypertension avoid use of adrenaline, use external drainage alone (as described below) to achieve detumescence.

3) If the penis remains erect, insert 21 G scalp vein needle into any one corpus cavernousm. Allow blood to drain passively (do not aspirate) into a clean tray, till it runs bright red and the penis detumesces partially. This may take 5-30 minutes. Now flush the needle with saline or dilute adrenaline solution and clamp the tubing. Watch for 10 minutes - the penis should remain partially detumesced. If it re-erects, continue drainage. Once detumescence is achieved, remove the needle and compress for 10 minutes. Observe the patient for 1 hour before sending home. Instruct him to contact the doctor immediately if the penis should become erect again.

### Interpretation of Diagnostic ICIVAD

(Using Bimix or PGE-1 and penile stimulation as discussed above)

1) A full, sustained erection after a low dose indicates normal penile haemodynamics (regardless of what other tests may indicate), thus the problem is then either psychogenic (usually), neurogenic (occasionally) or endocrine (very rarely). It is usually possible to distinguish between these by history and examination alone. Further tests are required only rarely.

2) A full, sustained erection after a high dose indicates either a psychogenic problem with marked anxiety or mild vasculogenic insufficiency which is compensated by the sustained, vasodilatory effect of the injection.

## THERAPY

Many problems will be resolved with sex therapy, counselling, education and reassurance.
Medical therapy has a limited role restricted to treatment of specific problems. Anti-anxiety and anti-depresant drugs when indicated and hormone therapy only if a clear-cut problem is identified [16,17].

*Self injection therapy:* Intra penile injection of vasoactive drugs has proved to be an extremely useful form of therapy. Intra penile injection of papaverine – phentolamine and/or prostaglandin EL produces a good erection in 80% to 90% of men. These men can learn to self inject themselves, then use injection at home to obtain an erection and have intercourse. Self-injection therapy can be used as a confidence booster for men with neurogenic or mild to moderate vasculogenic impotence.

### Oral Agents:

B) NON-HORMONAL, NON-INTRACAVERNOSAL;

There is a great desirability for the availability of non-hormonal, non intracavernosal medications in the treatment of sexual dysfunction. Of the following available treatment options for erectile dysfunction, none are without unappealing side effects:
1) *Sexual counselling* : Time consuming of unproven benefit in double studies. 2) *Vaccum* devices: Manual dexterity required, need to be removed after 30 minutes, interfers with ejaculation; 3) *Self injection:* Painful not spontaneous for many patients and partners; 4)*Microvascular arterial bypass surgery:* Limited candidates, 5)*Implantation:* Irreversible, surgical, associated post operative complications, unacceptable to many patients. Although much activity has been generated there is little available in the form of F D A – approved safe and efficacous non-hormonal, non-intracavernosal treatment options for erectile dysfunction. The following non-hormonal, non-intracavernosal treatments will be discussed: [9] 1) L-Arginine 2) Alpha blocking agents such as Phenotolamine (Alpha-1 and Alpha-2), Trazodone, Hydrochloride (alpha-1), Yohimbine Hydrochloride (Alpha-2) and Delequamine Hydrochloride (Alpha-2), 3) Apomorphine and 4) Phosphodiesterase Type V specific inhibitors.

### 1. L-Arginine:

L-Arginine is an essential amino acid and a nitric oxide precursor. Nitric oxide has been shown to be the neuro-transmitter in the efferent autonomic cavernosal nerves which is released following sexual stimulation. Nitric oxide has also shown to be the factor which is released following sheer stress forces from new arterial inflow along the lacunar space endothelial surfaces. Whether released from neural or endothelial sources, nitric oxide ultimately plays a major role in the induction of penile smooth muscle relaxation following sexual stimulation. Nitric oxide is synthesized from L-Arginine and molecular oxygen in the presence of the enzyme nitric oxide synthase and a PO2 level exceeding 55 mm Hg. Very few documented studies of L-Arginine use as a treatment for erectile dysfunction have been published. In one study, L-Arginine had been given to 20 impotent patients in a stable relationship. Placebo was given for 2 weeks and L-Arginine for 2 weeks.

## 2. Alpha-Blocking Agents—Phentolamine (Alpha-1 and Alpha-2)

Phenotolamine hydrochloride is a competitive alpha-adrenergic antogonist with similar affinity for Alpha-1 and Alpha-2 adrenoceptors. In addition, phentolamine can block receptors for serotonin. Phentolamine also has a direct, non-specific relexant effect on blood vessels. There have been several publications converning the use or oral phentolamine and the treatment of erectile dysfunction. Although most have been small studies in single institutions. In 1994, in an open label trial, Zornioti reported in impotent men the use of 50 mg of Phentolamine against 10 mg of Phenoxybenzamine (along acting Alpha Blocking Agent) 1.5 hour prior to intercourse. Forty two percent were able to erect for intercourse with phentolamine against 9% with phenoxybenzamine. In a single blind trial also in 1994, Zorgnitti compared 20mg buccal phentolamine with placebo give 20-30 minutes prior to intercourse. Thirty two percent were able to erect for intercourse with phentolamine while only 13% were able to erect for intercourse with placebo. Gwinup [19] in 1988 reported that 69% of men with unspecified impotence were able to penetrate 11/12 hours later following 50mg. oral phentolamine; only 3/16 (19%) of similar men responded to placebo. Brooks in 1992 reported that 2 impotent diabetic improved erections taking oral phentolamine.

### Trazodone Hydrochloride (Alpha-1)

Trazodone hydrochloride is a typical anti-depressant without antimuscarinic effects. It is selective inhibitor of central serotonin uptake and is associated with an increased turnover of brain dopamine. It has been demonstrated to have an alpha-adrenergic blocking effect in isolated human cavernosal tissue. The metabolite of trazodone is methycloropheylpiperzaine. This metabolite has also been demonstrated to have alpha adrenergic blocking effect on isolated human cavernosal tissue. In human placebo controlled trials, trazodone hydrochloride has been shown to be the first agent which statistically prolongs erectile activity in minutes during nocturnal penile tumescene studies when compared to placebo and trimipramine. Yohimbine, Alpha-2, adrenoceptor antagonist acting at presynaptic Alpha-2 adrenoceptors reduce the negative feed back of noradrenaline level. Like yohibine, this Alpha-2, adrenoceptor blocking is associated with the increased central and peripheral levels of norepinephrine. Thus delequamine has the associated cardiac and pressor effects of norepinephrine. Animal studies with delequamine have revealed increased sympathetic outflow (DOG), sustained increases in heart rate, cardiac work, cardiac output and 4-12% increase in the systemic arterial blood pressure. Delequamine hydrochloride is provided in twice daily dosing, has good bio-availability, linear pharmacokinetics, and a 5.8 hours life. Delequamine hydrochloride (upto 1 mg.), has been given to several thousand male subjects, part of a large multi-institutional international trial. The drug has not been shown to be more efficacious than placebo in the treatment of organic impotence.

In a recent study of 43 men with erectile dysfunction (39% psychogenic, 33% organic and 29% mixed, Albo and Steers reported on the safety and efficacy of treatment with trazodon hydrochloride. Of the 43 patients, 2 never initiated therapy, 3 discontinued in one week and 5 were lost to follow-up. 33 patients were available for study. In doses ranging from 50 mg to 100mg use of trazodone hydrochloride was associated with 64% positive erectile responses. Drowsiness, a common, side effect associated with trazodone hydrochloride, was noted in several patients which required dosage reduction.

### Yohimbine Hydrochloride (Alpha-2)

Yohimbine Hydrochloride an alpha-2, blocking agent, has long been considered an aphrodistic but its positive effect on erctile dysfunction has never been documented over placebo. Yohimbine Hydrochloride activity on penile erection is probably not based exclusively on the local erctile response. Yohimbine has low activity in isolated

erectile tissue studies and intracavernosal administrations have not resulted in erectile response. The presence of alpha-2, adrenoceptors have been demonstrated on non-adrenergic nitrenergic, nerves, especially associated with the cavernosal artery in penis. Their antagonism by Yohimbine may augment release of non-energic nitrenergic, neurotransmitters, which have been shown to increase arterial blood inflow into the erection tissue. Administration of Yohimbine has been shown to increase central levels of norepinephrine. The best explanation, for this drug effect is that central alpha-2 receptors are pre-synaptic on the adrenergic nerve and when activated, result in inhibition of norepinephrine release. Blockage of the alpha-2 receptors by Yohimbine results in excess central norepinephrine released. This explains the major side effects of Yohimbine, that is increased blood pressure, pulse, and anxiety impotence. In those with organic impotence taking Yohimbine, 43% claimed improved erections. In patients with organic impotence taking placebo, 29% reported a positive response. In patients with a mixed organic/psychogenic aetiology, those taking Yohimbine noted a positive response in 1/3 of cases.

**Delequamine Hydrochloride (Alpha-2)**

Delequamine Hydrochloride is an oral drug which is being developed for the treatment of male impotence. This Alpha-2, adrenoceptor antagnoist is 100 times more selective for the Alpha-2 receptor than Yohimbine.

## 3. Apomorphine:

Apomorphine has a direct central D-2 dopamine receptor agonist activity. In 1983, Vogel [17] reported that L-dopa therapy in the patients with Parkinson's disease resulted in penile erection in some cases. In 1988, Danjon utilised 0.25 – 0.75 subcutaneous apomorphine in healthy volunteers. There was enhancement of erection potentiated by visual sexual stimulations without any observed increase in libido. In 1987, Lal reported use of apomorphine, 4/8 achieved a full erection and 1/8 achieved a partial erection. In 1991, Seagraves utilized 0.25-1.0 mg subcutaneous apomorphine and reported that 11/12 impotent patients improved penile erection. Danjou, Lal and Seagraves observed that the dramatic side effect of apomorphine which is central activation and stimulation of the chemoreceptors trigger zone for nausea and vomiting. In addition, apomorphine in high doses (5mg) has been shown to cause respiratory depression. Otherwise other side effects of apomorphine have included yawning, drowsiness, lacrimation, flushing and dizziness. Such side effects have severely restricted research with apomorphine in the treatment of erectile dysfunction. In 1990, however, Morales and Heaton [10,11] described a sublingual form to apomorphine which has dramatically lowered the incidence of the major side effect in a large scale placebo-controlled, multi-institutional phase-III drug trial.

## 4. Phosphodiesterase type V specific inhibitors (Via GRA):[12]

A new oral drug is presently being investigated. The drug UK-92, 480 is a competitive and selective inhibitor of GMP type V Phosphodiesterase form present in corpus cavernosum smooth muscle cells. Relaxation of the corpus cavernosum smooth cells is mediated by nitric oxide and its second messenger GMP. This drug would be expected to improve penile erections by preventing the metabolism of the nitric oxide-mediated cGMP. cGMP vessels specific phosphodiesterase is also present in smooth muscle cells of blood vessels and in circulation platelets. The drug UK-92, 480 is also antithrombotic, antivasospatic in the coronary circulation and a peripheral vasodilator. Multi-institutional phase-III drug studies are presently underway for investigation of the safety and efficiency of UK-92, 480.

## 5. Local/Intraurethral/Sublingual applications:

Interest in the utilization of skin drug delivery systems such as patches and gels has been rekindled in recent years with the introduction of marketed products in patch form such as nitroglycerine (NTG), estraderm, estradiol, clonidine, and most recently nicotine habitrol skin patches. These delivery systems offer better therapy, fewer side effects and higher subject compliance [13].

Two studies have reported on the use of topical preparations of two vasoactive agents: nitroglycerin gel and minioxidil solution (Rogaine), in impotence. In the first study the investigators applied a 2% nitroglycerine (NTG) paste to the penile shaft of 26 impotent subjects and evaluated tumescence by a strain gauge transducer in the laboratory while the subject reported viewed an erotic video presentation. Eighteen out of 26 subjects reported an increase in penile circumference after nitroglycerin paste compared with vehicle. Color Doppler measurements also demonstrated an increase in vessel diameter and blood flow of the cavernosa arteries. The increase in tumescence as determined by the standard corporeal calibration during

nocturnal penile tumescence recordings. The same authors, in an unpublished observation, reported that the results from a similar experiment in 8 young, non-impotent subjects suggests that full erection is possible when using nitroglycerine topical paste. Nitroglycerin, however, produces severe headache in the majority of the subjects who use the skin patch for angina and other heart disease which makes nitroglycerin less desirable medication for impotent men. In the second, the investigator studied a 2% minioxidil solution. (Rogainer, UP John), under strict laboratory conditions in a double blind, vehicle-controlled trial of 33 impotent subjects of various etiologies and a 10% nitroglycerine paste as standard preparation. One (1) ml. of 2% paste was applied to the penile shaft. Rigiscan was used to measure the increase in penis diameter and rigidity whereas arterial blood flow was asserted by colour doppler sonography. The investigators reported the highest efficiency in spinal cord injured (neurogenic) subjects followed by the subjects affected by vascular causes such as arterial insufficiency. Although a significant increase in penile rigidity and diameter was reported, none of the subjects produced a full erection. The investigator reported that Minioxide was more potent than nitroglycerine paste or vehicle with fewer side effects and suggested that minoxide topical solution should be used as an erection "facilitator" but not as an erection producer.

Topical prostaglandin EL is presently being investigated in 2% PGEI, and 4% PGL 1 with nitroglycerine solutions. An enhancer for improved skin absorption had also been added. In 15 impotent subjects, the 2% topical solutions yielded a 33% improved erectile response with an average response time 28 minutes. In another 18 subjects, the 4% solution exhibited a 61% response with an average response time of the 4% PGEI, with nitroglycerine solution demonstrated 62% erectile response with an average response time of 12 minutes. Intrautethral PGEI [21b], is presently undergoing, multi-institutional phase-III studies for the treatment of men with organic impotence. Only MM PGEI pellets are dispensed in the distal urethra (after voiding). The distal shaft of the penis is massaged allowing for drug absorption into the corpus spongiosum. Approximately 20% of the intraurethral drug can be absorbed from the corpus spongiosum into the corpus cavernosum through a myraid of inter-communication distal veins. Although, 80% of the drug passes into the systemic circulation, when the drug is PGL 1 it has no systemic adverse reactions. To achieve penile erection, intraurethral, PGL 1, doses have been as high as 125-1000 UG (compared to 2-40 UG intracavernosally administered), safety and efficacy have been well reported. The system is called as M.U.S.E. (mediated urethral system for erection). The dose is started from 250 microgram. 3 years follow up results state 52-69% efficacy.

## ARTERIAL REVASCULARIZATION:

Arteriogenic impotence due to proximal vessel disease is best treated by aorotoilliac reconstruction

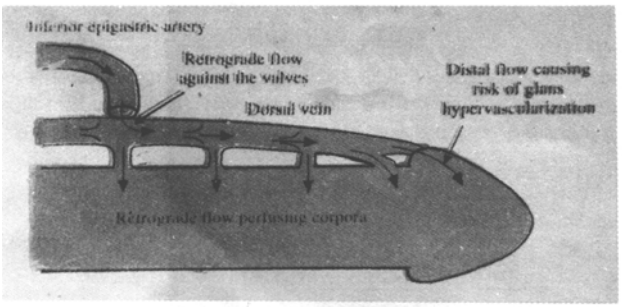

Fig. 5: Arterial Revascularization

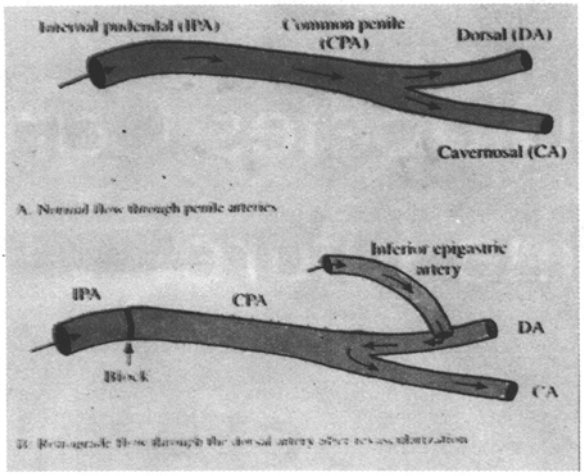

Fig. 6: Arterio – Arterial Anastomosis

using grafts and endarterectomy. Success would depend on the reconstructive procedure used and the status of the distal arterial tree and the cavernosal smooth muscle. When there is distal vessel disease, direct surgery on the penile vessel is required. Early attempts at cavernosal revasularization consisted of a direct anastomosis between the arterial source (inferior epigastric artery – I E G A), and the corpus cavernosum, the Michal-1 procedure. While some of patients did report of erections, many developed a pulsatile praispism due to the unregulated arterial inflow and eventually all the anastomoses got occluded. Subsequently, Michal developed another procedure, the Michal II technique (Michal, 1980) in which corporal revascularization was achieved by Anastomos I of IEGA to the dorsal artery of the penis. Cadaveric studies have shown that the main

source of cavernosal blood supply (and therefore the source of erection), are the cavernosal arteries. The dorsal arteries, mostly supply the glans penis. However, there are a variable number of perforations which enter the corporal cavernosa from the dorsal artery (Reiss, 1980); sometimes these may be large enough to allow significant inflow of blood into corposa. Usually, however these perforators are minor. Hence, the main, indication for revascularization of the dorsal artery is in the cases with an isolated block proximal to be bifurcation of the common penile artery, following a fractured pelvis, perineal trauma of isolated vascular disease. In such cases, blood flows from the IEGA into the dorsal artery and hence retrograde to the bifurcation of the common penile artery. From here it enters the cavernosal artery and then flows anterograde into the corporal spaces. In such selected cases the Michal II procedure and its variants work remarkably well with a success rate of 50% to 80% if there is no associated corporal dysfunction or neurological damage.

Recognising the predominance of the cavernosal arteries. Some investigators have directly revascularized the cavernosal arteries using the IEGA or a venous graft attached to the femoral artery, (Macgergor, 1982; Crespo, 1982). Though good results were claimed, occulsion of the anastomosis is common.

This concept was subsequently refined by Virag. In this procedure Virag anastomosed the IEGA to the deep dorsal vein at the base of the penis. The valve in the dorsal vein were ruptured, allowing the blood flowing retrograde in the direction of the glands. In the process, the corporal were perfused by blood flowing retrograde through the missary veins which otherwise drain blood from the corporal cavernosa into the dorsal vein.

Virag described a number of variations to adapt the procedure to each individual situation. These included ligations of the deep dorsal vein proximal and distal to the anastomosis, creation of the window between the deep vein and tunica albuginea of one corpus, and the use of a sapheneous vein and graft to revascularize the dorsal vein from the femoral artery. He found the procedure to be useful in both arteriogenic and venogenic impotence. Variations of this procedure have been described by other investigators with success rates varying from 15% to 90%. This success has been sustained during long term follow-up of upto 5 years. The authors have also described a variation where IEGA is anastomosed to the distal end of the deep dorsal vein to achieve anterograde blood flow. This procedure has a few technical advantages besides the anterograde perfusion. Venous ligation for "Venous leak" was popular a few years ago. However, long term results have been very disappointing and most centres have either stopped performing this surgery or offer it only to the selected young patients who understand the prognosis and are willing to undergo a later implant [11].

## PENILE PROSTHESIS : (Fig. 7, 8)

A penile prosthesis is a mechanical device which is permanently implanted into the penis to render it rigid enough for intercourse. Early attempt at penile implantation were only moderately successful. In 1936,

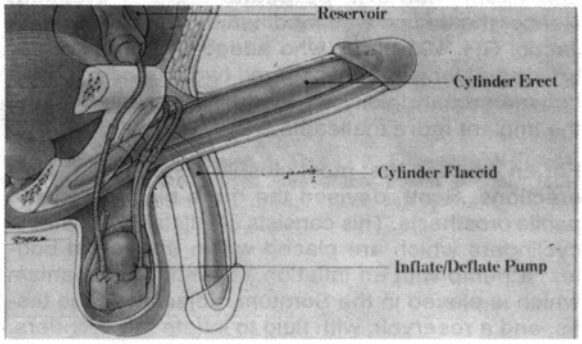

Fig. 7: Inflatable Penile Prosthesis

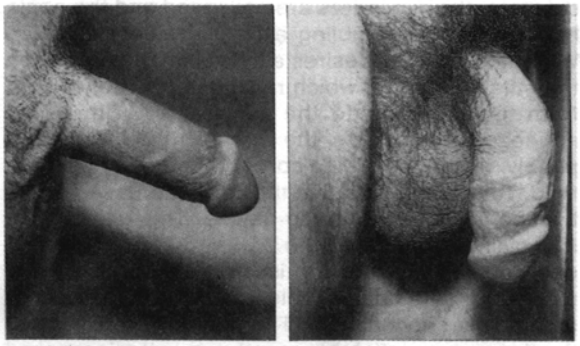
Fig. 8: Penile Prosthesis before and after inflation

Bogaras used rib cartilage to stiffen the penis. However, over a period of time, the rib was found to deform and resorb. In the 1950's Godwin used the help of a dentist friend to design a variety of acrylic penile implants. Although some patients did achieve successful coitus, the device was too hard to provide satisfactory results. In 1960, Behairi (Behairi GED, 1960. Loeffler RA, 1960) of Cairo reported his technique of placing a pair of polyethylene rods within each corpus cavernosum. Though the technique was apparently successful (in 1966 he reported treating a series of 700 patients) it never became popular due to the limited flexibility of polyethylene. The first truly satisfactory, widely used semi-rigid penile implant was the Small - Carrion implant reported, in 1975 (Small – MP, Carrion HM, 1975).

The small – carrion implant consisted of a pair of silicon rods moduled so as to fit the entire corpus cavernosum. The silicon imparted softness with flexibility while its placement in the full length of the corpus cavernosum imparted stability. The main disadvantage of the Small-Carrion implant was that the penis remained in a perpetual state of erection. Hence, the device was modified by Jonas (Jonas V, Jacobi GH, 1980)[22], who added a central core of braided silver wire. This served two purpose: it gave between axial rigidity while simultaneously making the implant more malleable.

For an erection that most closely resembles natural erections, Scott, devised the three piece inflatable penile prosthesis. This consists of inflatable deflatable cyclinders which are placed within the corpal bodies; a pump with an inflation – deflating mechanism which is placed in the Scrotum, adjacent to the testis, and a reservoir, with fluid to inflate the cylinders, which is placed in the lower abdomen behind the symphasis pubis, in front of the bladder. In the flaccid state, the cylinders are collapsed and the penis hangs loose, resembling a normally flaccid penis. When the patients desires an erection, he squeezes the inflatable pump which results in transfer of fluid from the reservoir to the cyclinders. With a few squeezes of the pump, the cylinders will fill up completely, expand to fill the corporal body and become rigid. To achieve deflation the patient presses deactivation valve in the pump device. This allows fluid into cylinder back into the penis to become flaccid one again. Thus erection is produced by the three piece inflatable device. This implant provides better rigidity and concealment. The main disadvantage of the three piece inflatable prosthesis is the increased complexity of design, cost, longer operating time and a greater risk of mechanical device failure. In fact, the 1970's model had an eventual re-operation rate for correction of device malfunction of upto 70%. However, the newer models incorporate many modifications, such as a seamless reservoir to avoid leaks, skinproof tubing, better connectors and reinforced cyclinders to prevent aneurysm, all of which have contributed to the mechanical failure rate of just 5% over 5 years.

The three piece implants have been modified into two piece implants and one piece, inflatable devices which are easier to implant. Penile prosthesis have been remarkably successful. The main problem has been their cost, with the malleable devices prices range from Rs.25,000 to Rs.40,000 and inflatable devices cost Rs.1,25,000 to 1,40,000.
All implants carry a small risk of infection for which adequate precautions need to be taken peri-operatively. Antibiotic prophylaxis is also required later on during dental procedure, other surgeries or if there is any infective focus in the body. Orgasm, ejaculation and fertility are not directly affected by a penile implants. Many have fathered children after receiving a penile prothesis.

**VACCUUM ERECTION DEVICES** can help produce an erection in those men who are unwilling to go in for more invasive therapies. Retention bands are especially useful in men with venous leak.

With the modern advances in diagnosis and therapy it is now possible to offer most patients of impotence a successful solution.

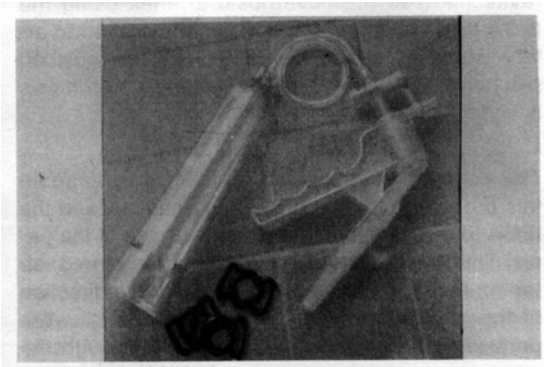

Fig. 9: Vaccume Suction Device

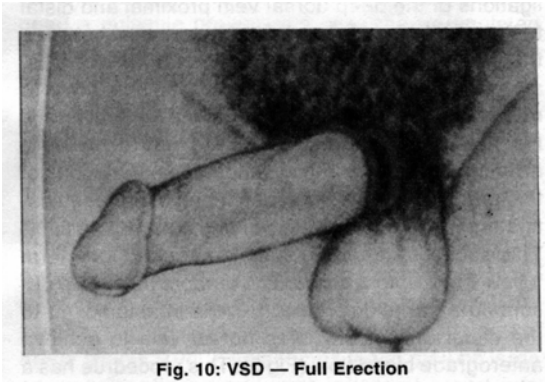

Fig. 10: VSD — Full Erection

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