Diagnostic and Therapeutic Milestones in Sexual Medicine

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“………… for if fluid is introduced into the hypogastric artery that leads to the corpora cavernosa, the penis is immediately erected …….. “

Regnier de Graaf (1641-1673).
1863: Untersuchungen üben die Erection des Penis beim Hunde

In a canine model, simulation of the nervi erigentes resulted in penile erection

Conrad Eckhard, (1822-1905)
THE BIRTH OF ANDROGEN THERAPY

The famous self-experiment of the French physiologist Charles Edouard Brown-Séquard (1817-1894) at the age of 72 years with several subcutaneous injections of a mixture of blood from the testicular veins, semen and juice extracted from crushed testicles of young and vigorous dogs and guinea pigs in 1889 was a first milestone of androgen therapy in the aging male although his “pharmaceutical” prescription must have been equivalent to a placebo.

NOTE ON
THE EFFECTS PRODUCED ON MAN BY SUB-CUTANEOUS INJECTIONS OF A LIQUID OBTAINED FROM THE TESTICLES OF ANIMALS.

By Dr. Brown-Séquard, F.R.S. &c.

On the 1st of June last I made at the Société de Biologie of Paris a communication on the above subject, which was published in the Comptes Rendus of that Society on June 21st (No. 24). I will give here a summary of the facts and views contained in that paper and in two subsequent ones, adding to them some new points.
Coming of Age of Sexual Medicine
Mechanical Devices

1913: Otto Lederer
First patented vacuum device

1983: Geddings Osbon
FDA approval for vacuum erection device
1918: Sergei Voronoff
Reported on transplantation of testicular tissue from a monkey into a human, claiming that this led to restoration of youth

1918: Victor Lespinasse
Treated impotence with implantation of cadaveric testicular tissue

Lespinasse V, Surg Clin Chicago, 1918
1922: Leo Stanley

- Performed 1000 injections of animal testicular extract into 656 humans

- 81 reported increased sexual stimulation

- 19 men had impotence and 12 benefited from the injection

Coming of Age of Sexual Medicine
Surgical Treatments

1873: Francesco Parona
Sclerosis of the dorsal penile vein with hypertonic saline

1902: JS Wooton
Ligation of the dorsal penile vein

1908: Frank Lydston
Ligation of all dorsal veins
53% cure in series of 100 men

Parona F. Giornale Italiano dell Malattie; 1873.
1920: Eugen Steinach
Ligation of vas deferens as a method of rejuvenation

1936: Paul Niehan
Vasoligation as a treatment for impotence

1936: Oswald Lowsley
Plication of ischiocavernosus and bulbocavernosus muscle

Steinach E. Pubertätsdrüse, Berlin; 1920.
Lowsley O. JAMA; 1936.

Niehans P. Lancet; 1936.
THE INSTITUTE OF SEXOLOGY IN BERLIN

In 1919 Magnus Hirschfeld (left, 1868-1935) established the “Institut für Sexualwissenschaften” (right) in Berlin. It was the first center of public information and education, treatment of patients and scientific research. Many scientists worked at the institute, e.g. Felix Abraham and Ludwig Levy-Lenz (transsexual surgery), Arthur Kronfeld (psychiatrist) and Bernhard Schapiro (first hormonal treatment of cryptorchidism). Due to the political circumstances Hirschfeld left Germany in 1930 and the institute was plundered and the library destroyed by the Nazis in 1933.
THE G-SPOT

The gynecologist Ernst Gräfenberg (1881-1957) from Germany was a pioneer of intrauterine devices since the 1920’s favoring a ring of coiled silver wire (right). He emigrated to New York in 1940, where he finally published his milestone article on “The Role of Urethra in Female Orgasm” in 1950. The anatomical area described by Gräfenberg was later named after him as the G-spot.
The biologist Alfred Charles Kinsey (1894-1956) from Bloomington, Indiana performed the first epidemiologic study on human sexuality collecting sexual histories from a large number of men and women, resulting in a final sample of around 18,000. The two volumes “Sexual Behavior in the Human Male” (1948) and “Sexual Behavior in the Human Female” (1953) are milestones in the literature on the anatomy, physiology and psychology of human sexuality.
1936: Nicolai Borgoraz

Penile reconstruction with rib cartilage in a tubed skin graft

The first penile implant to facilitate an erection was used in a phalloplasty procedure performed by the Russian surgeon Nikolaj A. Bogaraz (1874-1952) in 1936. He used the patient’s rip cartilage and in later years he even performed this operation in patients with morphologic intact penis but suffering from erectile dysfunction.
1950: Peter Scardino
Implanted acrylic implant

1966: G. E. Beheri
Report of 700 men who had undergone polyethylene rod penile prosthesis implantation

Coming of Age of Sexual Medicine
Gift of Urology
Coming of Age of Sexual Medicine
Gift of Urology
Coming of Age of Sexual Medicine

Arterial Pathology

ERECTION DYSFUNCTION DUE TO ARTERIAL VASCULAR OCCLUSION

In 1948 the French surgeon René Leriche (1879-1955) firstly mentioned arterial vascular impotence in thrombotic obliteration of the aortic bifurcation, a syndrome he had already described in detail in the 1920’s and which today is named after him. During the following time several strategies were outlined to save or reconstruct the internal iliac artery during abdomino-pelvic vascular surgery to maintain or restore erectile function.
1973: V Michal
End to side anastomosis between inferior epigastric artery and hole in tunica

1980: V Michal
End to side anastomosis between inferior epigastric artery and dorsal penile artery

Michal V, Kramer R et al, Rozhl Chir, 1973
Coming of Age of Sexual Medicine
Revascularization Surgery
Arteriography of internal pudendal arteries and revascularization of the corpus cavernosum in impotence of vascular etiology.

Ginestié J, Ginestié JF, Romieu A.

Coming of Age of Sexual Medicine
Revascularization Surgery
Coming of Age of Sexual Medicine
Revascularization Surgery
Coming of Age of Sexual Medicine
International Society for Impotence Research
Coming of Age of Sexual Medicine
Intracavernosal Injections
Dr. Brindley delivered a 1 hour lecture at an AUA meeting (4/18/83, 7:00 PM, in Las Vegas, Nevada

In that 1 hour Dr. Brindley, changed an entire field
Erectile Physiology (pre-1983)

Limited knowledge of penile erectile physiology

Polsters or cushions around penile vessels relaxed to let blood in and contracted to trap blood during sexual arousal

Erectile dysfunction treatments were limited
All this changed on Monday April 18, 1983, 7:00 PM, in Las Vegas, Nevada at the AUA’s 78th Annual Meeting

The American Urological Association (AUA), through the affiliate Urodynamics Society, invited Professor Giles Brindley, an innovative British neurophysiologist, to lecture on the confusing state of erectile physiology
Twelve other speakers on 4/18/83 7:00 - 9:30 PM - **no one remembers any of them**
Those in attendance Monday, April 18, 1983 7:00 - 9:30 PM Urodynamics Society, Ballroom C, Hilton Hotel, Las Vegas Nevada, 78th AUA (based on survey)

Paul Abrams
David M. Barrett
Arnold Belker
George S. Benson
Larry Beutler
Jerry G. Blaivis
Saul Boyarsky
Andrew Bruce
Paul Carpentier
Roy Correa
Joe Corriere
William L. Furlow and wife Venessa
Donald Gleason
Irwin Goldstein
Ciril Godec
Han Hanafy
Frank Hinman
Wytze Hoekstra
Ted Keogh
Robert J. Krane and wife Bambi
Laurence Klotz
Robert Levin
Larry I. Lipshultz
Tom Lue
David Mitcheson
Abdel Mohamed
Alvaro Morales
Jacek Mostwin
John Mulcahy
Earl Nation
Leroy Nyberg
Kevin O’Connell
Theodore Ongaro
Udo Jonas
Pompeo
William L. Perry
Inder Perkash
Shlomo Raz
Jim Roberts and wife
Harold M. Reed
F. Brantley Scott
Ira Sharlip
Naeem M. Siddiqi
Mike B. Siroky
William Steers and wife Amy
Jacques Susset
Emil A Tanagho
Andrew Von Eschenbach
Hans de Wall
George Webster
Alan J. Wein
Steven K. Wilson
Norm Zinner
Adrian Zorgniotti
The 1983 AUA meeting in Las Vegas was probably the most memorable meeting I have ever attended. Not only was this the first time that I attended the AUA, but also I won the first prize AUA basic research essay contest on neurostimulation and physiology of penile erection. I was really excited to attend the evening session of the Urodynamics Society, because my mentor, Dr. Tanagho, was scheduled to give a lecture on penile physiology. When I looked at the program, I saw Giles Brindley was also scheduled to talk about penile physiology. It was a big meeting room and crowded with people. I managed to get a good seat about 20 rows from the podium, so I could read every single word on the slides. At this meeting, everybody dressed formally with suits and ties.

Tom Lue (6/13/06)
All of a sudden, I saw a gentleman with running shorts went up to the podium to start his talk. This English gentleman began to talk about his research in penile physiology. He showed many slides of stages of penile erection from flaccid state to full erection. And to my surprise, he confirmed those were his own penis at different time points after stimulation. He confessed that he injected himself before he came to the meeting room and then dropped his pants to show his erect penis. He then stepped down from the podium and asked the audience to palpate it to be sure that it was not from a penile prosthesis.

Tom Lue (6/13/06)
I was there at AUA meeting in Las Vegas, with a friend urologist Adel Mohamed, when a friend told us about a lecturer with training suit discussing self injection. We rushed to the meeting where Dr. Brindley was on the podium with apparent" BULGE" in the front of his sweat pants. He was very serious about self injecting his penis prior to the lecture with a substance we did not get its name. He walked around asking the audience to touch his erect penis to verify his statement. I don't recall any one touching him. By pure coincidence, Dr. Brindley sat next to us. My friend Adel and myself chatted with Dr. Brindley & asked him to write the medicine and dose he used. Dr. Mohamed gave him his appointment card & he wrote by his *handwriting* the phenoxybenzamine dose & upcoming article.

Han Hanafy (5/30/06)
Handwriting of Dr. G.S. Brindley while in his jogging suit after the first world ICI at the AUA meeting Las Vegas 1983
I thought that Brindley was just the ultimate in British eccentricity on that night in 1983 in LV. Some of the crowd was offended and some people thought it was he was nothing more than a sexual exhibitionist. I think that I was sitting next to Arnold Belker at the event in 1983. When he told Brindley that phenoxybenzamine was not approved by the FDA because of tumors in lab animals, there was a great laugh in my area of the audience and a lot of jokes about how Brindley's "twinky" was going to get cancer or fall off.

Ira Sharlip (5/29/06)
I was at there on Monday evening at the 1983 AUA meeting in Las Vegas when Giles Brindley showed up in a jogging suit and dropped his sweatpants 20 minutes into his talk showing the world his erection with slight downward curvature created by intracorporal injection before going on stage. I told Joe Segura and he mentioned the episode when giving the highlights of the previous day at 7:30 the following morning.

John Mulcahy (5/27/06)
I was there but since there is a 6 in front of my age, so I may not remember the details.

I always thought it revolutionized the treatment of impotence. For the first time we had a treatment besides prosthesis that we could offer patients. You remember we had only Yohimbine that was about as powerful as a teaspoon of honey. Because of the way he popularized it (by shocking the urologic community) knowledge of the chemical's effectiveness became widespread quickly and changed the paradigm of impotence treatment.

Steven K. Wilson (5/29/06)
Coming of Age of Sexual Medicine
Intracavernosal Injections
Coming of Age of Sexual Medicine
Psychology
Erection Hardness Scale (EHS)

1. Penis is larger but not hard
2. Penis is hard but not hard enough for penetration
3. Penis is hard enough for penetration but not completely hard
4. Penis is completely hard and fully rigid

**69 percent** of all attempts at sexual intercourse by the men receiving sildenafil were successful.

**22 percent** of all attempts at sexual intercourse by the men receiving placebo were successful (p<0.001)
Coming of Age of Sexual Medicine Pharmacology

1993: Intracavernosal Alprostadil (Caverject®)
1997: Intraurethral Alprostadil (MUSE®)
1998: Sildenafil (Viagra®)
2001: Apomorphine (Uprima®)
2003: Tadalafil (Cialis®)
2003: Vardenafil (Levitra®)
Coming of Age of Sexual Medicine
Epidemiology
Coming of Age of Sexual Medicine
Gift of Sexual Medicine
Coming of Age of Sexual Medicine
Gift of Sexual Medicine
Coming of Age of Sexual Medicine
Gift of Sexual Medicine
Coming of Age of Sexual Medicine
Gift of Sexual Medicine
Coming of Age of Sexual Medicine
Gift of Urology
Coming of Age of Sexual Medicine
Gift of Multidisciplines
Shockwave therapy may be one day be considered as a safe and effective disease modification strategy.
LiSWT- Meta- Analysis of RCTs

• Meta-analysis of 7 randomized controlled trials using LiSWT for ED reporting IIEF-EF scores
  • 602 subjects
  • Age – 60y
  • Follow-up – 5 months

• Improvement in IIEF-EF score was 6.4 (Treat) vs. 1.6 (Sham)

Clavijo RI, Kohn TP, et al J Sex Med. 2017
Technical characteristics
results of meta-analysis

◆ The studies using higher energy flux density (EFD; >0.2 mJ/mm²) resulted in significantly increased IIEF (mean difference [MD]: 2.86; 95% confidence interval [CI], 1.54–4.19; p < 0.0001)

◆ The improvement of IIEF was better for the group with EFD 0.09 mJ/mm² compared with EFD 0.1–0.2 mJ/mm², although it did not reach statistical significance.

◆ The studies delivering more shock waves per treatment (5000 vs 1500) resulted in an increased IIEF (MD: 2.86; 95% CI, 1.54–4.19; p < 0.0001).

◆ The studies with total course of treatment <6 wk revealed significant IIEF increase (MD: 2.11; 95% CI, 0.98–3.25; p = 0.0003) versus studies with longer courses of treatment (9 wk).

Shockwave therapy has been studied in numerous ED patients and demonstrates safety and efficacy.
Coming of Age of Sexual Medicine
Gift of Woman’s Sexual Health
Coming of Age of Sexual Medicine
Gift of Multi-disciplines - Women’s Sexual Health
Coming of Age of Sexual Medicine
Gift of Multi-disciplines - Women’s Sexual Health
Coming of Age of Sexual Medicine
Gift of Multi-disciplines - Women’s Sexual Health

Three Testosterone-Dependent Organs in the Vestibule

- Glans clitoris
- Minor Vestibular Glands
- Peri-urethral tissue – G-spot

Pre-Testosterone Treatment

Post-Testosterone Treatment
First Drug Approved for Women

Ospemiphene

SERM (estrogen receptor agonist/antagonist)

Binds to ER alpha, ER beta – high density in vestibular and vaginal tissues

approved as an oral agent for treatment of pain during sexual activity in menopausal women
Timeline for Flibanserin

- **1995**: Phase 1 studies
- **1996**: Phase 2a MDD study
- **1997-1998**: Phase 2b MDD trials
- **1999-2001**: MDD trials with ASEX
- **2002**: PoC trials for HSDD in women begin
- **2004-2006**: FDA sets requirements for clinical trial measures (draft guidance) including separate trials for pre- and postmenopausal women – no established pathway to approval
  - Requires SSEs as co-primary endpoint
  - Rejects SIDI-F – requires daily desire item (co-primary) and desire related distress (2ndary EP)
Timeline for Flibanserin (cont’d)

- **2004-2006**: Validation of scales and e-Diary including requirement of a simple screening tool for PCPs (DSDS validated)
- **2007-2008**: Pivotal trials and study of maintenance of effect conducted
  - One co-primary endpoint (eDiary) fails at final time point in one of the trials (blind not broken on other studies)
- **2010**: FDA Ad Comm to determine whether to allow change of co-primary endpoint on desire to FSFI-Desire subscale – rejected
- **2010**: FDA Draft Guidance on FSD withdrawn
Timeline for Flibanserin cont’d

- **2010**: BI halts development including on-going studies (postmenopausal women, use with SSRIs/SNRIs in MDD)
- **2012**: Sprout Pharmaceuticals established and performs trials required in FDA complete-response letter (validated FDFI-Desire subscale, drug interaction study, excessive alcohol study). FDA allows use of FSFI-D to measure desire
- **2014-2015**: Resubmission of flibanserin met with new requirements by FDA. Sprout appeals, and FDA relents
- **2015**: FDA Ad Comm votes 18 - 6 for approval, but FDA requires REMS not supported by science
FDA Approved Intervention: HSDD

- Flibanserin (5-HT$_{1A}$ post-synaptic agonist and 5-HT$_{2A}$ antagonist) 100 mg daily at bedtime approved 8/18/2015 at 6:30 PM EST for generalized, acquired HSDD in premenopausal women
  - 50% of women respond
  - Stop if no effect after 8 weeks$^1$
  - Requires REMS registration at www.addyirems.com

- Also safe / effective in postmenopausal women, but not yet approved$^2$

$^1$FDA Briefing Document:

Coming of Age of Sexual Medicine
Gift of Multi-disciplines

Sexual medicine has traveled the road from trial and error and anecdotal evidence, to a place where it now exists as its own field based on evidence.
Coming of Age of Sexual Medicine
Gift of Multi-disciplines

Just look at the number of people who need our help ...

and look at the volumes of new research despite the paucity of government funding in this area ...

Every day we are privileged to be writing new sexual medicine history, and we should all be proud to be part of it