

2

The History of Modern Sexual Medicine

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When asked to prepare this chapter I was honored, but faced a rather daunting task of developing a chapter on the history of sexual medicine of where to begin. I then decided that to me one of the turning points of the development of this area as more scientific in nature occurred with the publication of the seminal work of Kinsey [1], and Masters and Johnson [2, 3], where their close observation studies of couples sexual interactions and intense history gathering of these individuals began to take sexual activity out of the realm of mystery, interactive intrigue, and intense psychoanalysis necessary to provide relief for these couples. Thus I added the word “modern” to the title. As an example of getting back to some of our scientific roots I remember an example that Masters gave in a talk at Tulane while I was a medical student there in the mid 1960s of solving of a sexual dilemma for two Ph.D. individuals, who after seeing many specialists and both having what appeared to be super normal fertility potential as individuals were simply asked about their copulatory pattern in detail. They had been going to bed and “sleeping together” at the correct times but rather surprisingly naïve never actually having intercourse. What Dr. Masters stressed that he did not find this particularly unexpected in this highly educated but rather sexually uninformed couple but that they had found each other on the campus. I remembered this as an early lesson to me the importance of getting details on the history of any medical condition, particularly to those that involve sexual matters, without any preconceived notion of what the answer to such obvious question may reveal. Their infertility was promptly solved with just a mild intervention process.

As I also prepared to develop this chapter, I was reminded of a challenging but very fun educational activity of one of my undergraduate courses entitled History of Biology in which the professor had divided the centuries in six required times in which we as students were required to develop an essay during the semester of each of these periods expressing the conflict of either Mystery or Religion versus

Scientific thought as it reflected on the culture of that particular time. What struck me for most of these time periods the dominant and accepted norms were often emanating from mystery or religion and the upstart scientific realm was often fighting an uphill battle. It is sometimes difficult to write as history such a new and continually developing field as sexual medicine since the field as a science is less than a century old. I will try to include what I think have been the most significant events that have driven this field into the more scientific realm that it has become today. Now, to quiet some potentially critical points of view, I by no means intend to indicate that sexual medicine disorders become science if only “medicalizing” the diagnosis and management of these distinct disorders as simple or isolated individual approaches is the determining factor that makes this field scientific. We all must never forget that most of sexual disorders or problems are not only a concern for the individual but also for a “partner(s)” as well and that we all who work in this area should be ever mindful of our inadequacies of truly dealing with this inter-active and intra-active nature of the management of sexual disorders. So even some of the magic of dealing with these problems prior to Masters and Johnson era still have a bearing of importance for us. I will try to highlight seminal scientific approaches in this young field as it occurred in time. I, by no means, have the ability to cite all of the important contributors in this field but have included those who have been dominant in pushing us into a more scientific field.

As we get into the modern history much of the early science centered on erectile dysfunction (ED) but other areas are highlighted in the chapter. Each major division indicated by bold title could possible lead to its on full chapter on the history so this is a very succinct attempt at history of sexual medicine in general. I have tried to select references that include many who have contributed to the field in their bibliographies which cite major contributors in the field.

Observational Studies Leading to Major Changes in the Therapeutic Approach to Sexual Disorders

Although the observations of Masters and Johnson [2, 3] gave a more documented and descriptive nature of sexual physiology it was followed soon by the realization that simple treatment behavioral modification did not work in all individuals because of the overlapping secondary individual and partner interactive processes playing a “resistant” to cure so therefore a new paradigm for therapy was developed that combined behavioral modification of sexual symptoms of classic therapy with brief, active psychodynamically oriented management of the patient’s resistance [4]. A third seminal development in understanding human sexuality from a monistic process to the development of a triphasic paradigm was proposed by Dr. Kaplan in the late 1970s [5, 6]. Even this triphasic stepwise nature of sexual reactivity has been recently modified (see below). This triphasic nature of the sexual response moved the evaluation and treatment from a simple clinical entity to more complex interactions in the one individual to several interacting components but also to a series of interactions between the partner’s sexual response as well. An example of the inadequacy of treating a man for ED without recognizing the patient’s main problem may be hypoactive sexual desire, which if not addressed as well, would lead to therapeutic failure to treat the impotence [7]. Michael Perelmann about 7 years ago nicely summarized a new integrative approach to the management of sexual dysfunction [8].

A New Focus on Vascular Disorders of the Male Genitalia

At about the same time that this new focus on the diagnosis and therapy was occurring in the sexual therapist realm two studies emanated out of Europe focusing on recognition of possible vascular restoration occurring with pelvic vascular surgery for impotence [9]. The other publication was the elegant radiological evaluation of the intracorporal and pelvic vasculature via specialized arteriography [10]. These caught the attention of two key clinical investigators at that time, Adrian Zorngiotti of New York City and Gorm Wagner of Denmark, who also had performed some elegant observational studies of physiological changes in the female genitalia and the male corpus cavernosum, to team as leaders in preparing a meeting in New York City in the fall of 1978 to discuss some of this new cutting edge treatment and evaluation of impotence which sequentially became the biennial meeting for at first impotence, then all of male sexual dysfunction to

eventually sexual dysfunction in men and women under the current organization, the International Society for Sexual Medicine [11]. More detailed historical data regarding Dr. Zorngiotti can be found in Dr. Lizza’s 2005 article [12]. At the 1978 meeting in New York City 188 revascularization procedures, mostly inferior epigastric artery to the corpus cavernosum (Michal I) were presented from 7 international sites with as high as 77% positive functional result [11]. The sophistication of presentations led to plans to address more science associated with penile erection and treatment of impotence at a second meeting in Monaco in 2 years in 1980. See Ref. [10] and the book that also was published on data from this initial 1978 meeting [11, 13]. By the time of the meeting in Monaco results of revascularization of the corpora cavernosa for impotence was reported from nine new centers in addition to Michal’s group, most now using the Michal II, inferior epigastric artery anastomosis to the dorsal artery of the penis [11]. A unique revascularization procedure using the inferior epigastric artery to the deep artery of the corpora were also reported in a few cases from Latin America and the United States but long term follow up of these procedures and later reports of similar surgeries never appeared again. This revascularization group also included the first report of the Virag Technique of deep dorsal vein arterialization for vascular treatment of erectile dysfunction [11].

It is beyond the scope of this brief history of evolving sexual medicine to continue where this initial enthusiasm for penile revascularization treatment led but long term results were certainly mixed with major occlusion eventually for the revascularization arteries, probably due to some of the need for physiological runoff for successful revascularization and the non-physiologic connections such as to deep dorsal vein without runoff established to the corpora cavernosa itself or direct connection to the corpus cavernosa. Today only specific traumatic damaged pelvic internal pudendal arteries or the branches to the corpora verified by specific sophisticated pelvic arteriography (with ability to use the inferior epigastric artery as a donor artery to anastomotic vessels beyond the specific damage site such as dorsal arteries with definite branches to the corpus cavernosal deep artery serving as run-off vessels) should be the patient of choice for revascularization procedures. These are usually young patients with specific pelvic trauma. Certainly arterial damage is more generally small vessel disease in the corpora cavernosa itself now proved by more anatomical and physiological studies particularly in those patients with generalized vascular disease such as arteriosclerosis and microvascular injury in association with such diseases as diabetes mellitus (DM). This medical approach tended to blossom with overenthusiastic surgeons before some of the needed anatomical and physiological sciences of the corpus cavernosa were well understood.

The Ultimate Reconstructive Surviving Treatment of Erectile Dysfunction

Before the “new focus” on understanding the nature of the tissue of the penis erectile tissue and the 1978 awakening of alternative vascular repair for this disorder, a group of surgeons from various regions of the world had gradually developed the replacement of the physiologic process of erection with penile prostheses. This progressed from several types of artificial “os penis” devices being placed in the penis, but not into the corpora cavernosa itself, to intracavernous rigid and semirigid devices placement to various hydraulic intracavernosal prostheses. Semirigid, and two or three piece devices persevered to remain a major therapeutic success story of the treatment of ED. The reader of this historical piece is encouraged to read previous selected publications which well spell out this history of prosthetics for the treatment of ED [14]. One persistent characteristic of this modality is the constant nature of the surgeon and engineer to improve these devices to lessen mechanical wear, to develop infection resistant materials to aid in that devastating end point prevention, to improve the surgical techniques for placement of the devices, and to develop sophisticated salvage procedures when failure occurs. Key early pioneers in this field include Brantley Scott, William Furlow, Steve Wilson, Carl Montague, and Gerald Timms from Minnesota. At the second international meeting on impotence in Monaco in 1980, this area was highlighted in the program. A supplement to the *Journal of Sexual Medicine* in November, 2015 presents a review of historical papers with commentary in penile implant surgery [15]. Also another history review was published in sexual medicine reviews [16].

Intracavernosal Injection Therapy Treatment for ED

By the time of the 1982 third meeting on penile revascularization in Copenhagen, and certainly by the fourth meeting in Paris 1984, a new dominant therapy for ED was developing rapidly, injection of vasoactive agents into the corpus cavernosum [17, 18]. Another rich historic narrative on injection therapy from its beginnings can be found in a chapter from a Wagner and Kaplan 1993 publication [19]. Giles Brindley and Ronald Virag were the early pioneers in this field in 1982 and 1983 [17]. At first Virag proposed intracavernous injection therapy as an office procedure but auto-injection at home was proposed by Zorgniotti and LeFleur in a publication in 1985 [20]. At the fifth international meeting in Prague in 1986 the introduction of prostaglandin E-1 as the newest injection agent was made in laboratory and patient studies were presented from

Singapore, Japan, and Vienna, Austria [17, 18]. A 3 year follow/up of 69 patients using self-injection of prostaglandin E1 was reported from Finland in 1999 [21]. In 1996 intra-urethral prostaglandin E1 was approved but its efficacy was less than injection therapy [22].

One cannot discuss the history of injection therapy without citing a most seminal review article in the field by Junemann and Alken in 1989 [23]. The major agents used in diagnostic studies and therapy are two- or three-agent combinations using papaverine, phentolamine, or PGE-1 or using one of two FDA-approved PGE-1 agents alone [18]. Although a highly successful therapy for the treatment the invasive nature of the treatment is not well accepted by all patients and the long term dropout is still relative high. To demonstrate the rapid spread of this treatment for ED, at the 1984 meeting in Paris there were only five presentations dealing with intracavernous treatment for ED and in the subsequent 1986 and 1988 meetings there were over 45 presentations on the same subject [17]. Pharmacologic agent injection also became a major part of some of the diagnostic procedure as discussed below. The use of injection therapy for diagnosis, evaluation, and treatment of ED has been recently reviewed [24].

The Other Vascular Therapy for ED

By the time of the third and fourth meetings of the international group in Copenhagen in 1982 and Paris in 1984 some therapeutic and diagnostic studies stressing the veno-occlusive mechanism of erection were being addressed. Our group from Tulane University in New Orleans reported at the fourth international meeting in Paris in 1984 a dynamic corpus cavernosography [25]. We, in the introduction to that paper, discussed some of the early venous surgery for ED by Lowsley as early as 1953 and we presented some of our early vein surgery patients. We also credited early modern pioneers of venous surgery in the modern era, Ebbehof, Wagner, and Virag. In 1990 we presented an article on venous ligation surgery for venous leak in which we reviewed the earlier contributors and the then known results from around the world [26]. However long term results of this type of surgery were not sustained overtime mainly because it became apparent that veno-occlusive disorders were mostly the result of fibrotic changes in the sinuses of the corpora cavernosa and addressing the external veins would not change the lack of veno-occlusion which was dependent on total relaxation of the corpora sinuses. This type of surgery is now reserved for rare congenital venous defects in the wall of the corpora cavernosa and some rare cases of trauma or iatrogenic damage to the tunica albuginea.

The Other Early, But Less Sophisticated, Solution for ED

Another treatment for erectile dysfunction with origins predating the 1970 by patents but significant papers did not appear until 1986. Although not as sophisticated the modality still persists as an option for ED treatment. These were the vacuum erection devices which history has been well described by this author in a previous publication [27]. Early pioneers and authors of papers in this field include Perry Nadig and Roy Witherington. Although a rather crude solution the noninvasive nature of the treatment persists and is highly successful for many couples. This solution works best when both partners truly accept this as their “best choice” for ED.

Anatomic and Physiologic Studies in the Development of the Science of Sexual Medicine

Following the first two meetings of what was to become the International Society of Sexual Medicine in Monaco in 1980 and Copenhagen in 1982 there was an emphasis to better understand the anatomy and physiology of the corpus cavernosa of the penis. It would be impossible, for it would result in a very long chapter in itself to recount all of the discoveries that emanated from the various laboratories around the world. In 2003, some of the key pharmacological and physiological studies were included in the 102 references from a book chapter by Tom Lue’s group [28]. A very seminal work by deGroat and Steers outlining the key neurological pathways involved in the reproductive tract should be mentioned since that author was not included in the comprehensive list in the aforementioned bibliography in the Lue group article [29]. Another source of key historical participants in the basic research can be found in the basic science section of the textbook published in 2009 [30]. It would take myriads of pages and references to do the key basic science discoveries justice in this rather broad history perspective.

Suffice it to say, that all of this work described some of the central and spinal cord pathways involved in the initiation and maintenance of sexual activity. The anatomical studies clearly showed the vascular anatomy that fed the very “modified-capillary” connection between arteries and venous called cavernosal sinuses and the relaxation of these filled spaces to produce veno-occlusion dependent on an elastic and intact tunica albuginea. Most importantly the molecular nature of what happened to result in erection and detumescence led to an understanding of NOS and the initiation of Intracavernosal smooth muscle relaxation via nNOS release of nitric oxide with maintenance by shear force eNOS which

resulted in relaxation of the smooth muscle of the sinus spaces, with intra chemical messengers through GAP junctions to produce a coordinated relaxation with calcium changes in the cell. Once a sympathetic release following orgasm, the mostly activated cyclic GMP dependent system was returned to a contracted state with key input from enzymes, primarily phosphodiesterase 5. The normal tonic contraction of the penis in the flaccid state was maintained by such systems as the Rho-kinase system.

Measuring the Problem: Development of Epidemiology

Understanding the incidence and prevalence and developing key definitions is crucial in understanding the nature of sexual disorders in the population. These areas are key to establishing this field as science. There have been four international consultations regarding sexual function, but the first focused only on males. In the second and third International Consultation in Paris in 2004 and 2009 and the fourth international consultation in Madrid in 2015 epidemiologic data for sexual disorders in men and women from data collected from the mid 1990s until the most recent time before the meeting were evaluated by the panels making up this committee. Articles which reference lists include the main contributors in the field were selected from the literature which met evidence-based criteria and the results are best summarized in four articles and one book chapter which the reader of this brief history are referred [31–35]. It is the epidemiological data that helps establish the now established fact that arterial erectile dysfunction can be a harbinger for cardiac arterial disease. Also the strong association with diseases such as diabetes mellitus has prompted myriads of anatomical, physiological, and molecular studies of this disease effect on the corpora tissue further clarifying treatment of this disorder.

History of Key Diagnostic Study Development in Sexual Medicine Science

At the first meeting on arterial revascularization the exquisite work of pelvic arteriography of Ginestie were presented without some of the modern sophisticated technical aspects of radiography [9]. We published an updated discussion of radiology of ED in 1990 from the Mayo Clinic group [36].

Erectile function during REM sleep was as a measurement of impotence was originally presented by Karacan in 1970 [37]. He was one of two featured guest contributors to the meeting in Monaco of the international group

interested in ED which had convened in 1980 to further review corpora cavernosa revascularization. His early studies led to the development of the Rigiscan device which became an important diagnostic tool after this time [38]. After the development of color duplex Doppler studies of the corpora cavernosa the use of rigiscan diminished in importance but still remains an important part of evaluation of response to pharmaceutical agents in trial studies and some still think it crucial in the workup of ED. Using video sex stimulation erections and nocturnal erection measurement Slob et al. in 1990 reported their early result and follow-up with the use of penile vibration during the video sessions [39, 40].

Irwin Goldstein's group in Boston was a key contributor to development of dynamic cavernosometry and cavernosography as evaluation tools of the venous function of the corpora cavernosa. One of their key presentations appeared in 1987 [41].

After the development of injection agents, Tom Lue presented the concept of using penile color Doppler ultrasonography in 1985 [42]. At Mayo clinic in 1988–1999 a team of urology and radiology published several key papers on penile arteriography and the use of color Doppler ultrasonography [43–45]. In the AJR volume in 1989 in which the Quam article appeared [43] four other groups reported their early work on the use of color Doppler evaluation of impotence. Recently, in a paper by Sikka et al. standardization of color duplex Doppler studies was proposed [46].

As the field became more scientific there was a need for questionnaires to assess sexual disorders and two of the most successful validated instruments were the International Index of Sexual Functions (IIEF) and the Female Sexual Function Index (FSFI) first presented as publications in 1997 and 2000 [47, 48]. The design and development of such questionnaires is discussed in a book chapter in 2009 [49].

Major Breakthrough for Treatment of ED: Oral Pharmacotherapy

In March of 1998, sildenafil citrate, the first orally delivered selective PDE-5 inhibitor was approved by the United States Food and Drug Administration (FDA) for the treatment of ED. This class of drugs was an initial candidate antianginal agent but this medication and the many that came after it literally turned the tables on the management of ED because of its widespread effective use. An excellent reference of historical significance for the first 5 years of use of these compounds can be found in a book chapter by Harin Padma-Nathan [50]. In that same book put together by Dr. Gregory Broderick other chapters present more about this class of pharmaceuticals.

Other Than ED: The Science of Peyronie's Disease, Priapism, and Ejaculation Problems

Most of this discussion of the history of modern scientific sexual medicine has focused on ED but equally important for sexual disorders in men has been the science during the last years for understanding, diagnosing and treating other sexual problems in men. These areas include Peyronie's disease, priapism, and premature ejaculation.

In Peyronie's disease basic science studies have led to more scientific treatment of the local plaque prior to moving to the traditional surgical therapy of either plication procedures, excision of plaque with graft, or penile implant surgery [51, 52].

Priapism has been classified into ischemic or non-ischemic types and basic science studies have clarified some of the molecular changes in the cavernosal tissue such as changes in enzyme milieu in priapism associated with sickle cell disorders. An excellent review from Hellstrom's group includes priapism in males and females [53].

Premature ejaculation has been better defined, some central controls understood, and a more scientific approach to its management is now available. See the recent comprehensive review by Chris McMahon to view an historical summary of this disorder [54].

An excellent review of pathophysiology and management of delayed ejaculation has recently been published in 2016 [55].

In 1999, my colleague, Tom Mills and I reviewed the literature on the role of androgens in the maintenance of the erectile response citing in that article a number of studies [56]. Maggi's group in 2009 published an excellent review of the endocrinology of male sexual function [57]. Recently a process of care paper was published from the International Society for Sexual Medicine in their journal in 2015 [58]. From the fourth international consultation on sexual medicine a paper was published reviewing the literature supporting endocrinologic control of men's sexual desire and arousal/erection [59].

Catching Up: The Science of Sexual Medicine for Disorders in Women

At the International Meeting in Australia in 2000, it was recognized that the society needed to focus on the emerging science associated with women's sexual health, so for the first time a section of the program was entirely on women's sexual health issues. At the international meeting in Argentina in 2004 the organization changed its name to the current International Society for Sexual Medicine reflecting the need to focus on sexual medicine in both sexes. Soon after that the International Society for the Study of Women's Sexual Health was founded.

Some key papers that establish the science of sexual function and dysfunction in women are included in Refs. [60–67].

In fact, the first medication for a sexual dysfunction in women, flibanserin in premenopausal women, has recently been released [68, 69].

History of Sexual Medicine Science Drives Us to Optimal Treatment or We Are Not There Yet

The history of science of sexual medicine is not over and is not stagnant. Gene therapy and regenerative medicine developments to prevent damage to crucial sexual tissue or treat specific disorders such as ED are already developing. Penile transplant surgery is being pursued as a real possibility. Transgender medicine is now developing into a more stable scientific identity. As more understanding of the brain and mid-brain science of sex is understood perhaps designed medication to affect these areas may become reasonable. Finally, we can never stress enough, the importance of treating the couple for sexual disorders for epidemiologic data clearly shows this and the interaction between sexual partners is as paramount as treating individual disorders. History moves on.

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