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Perspective

The History of Endometriosis Preceding Sampson

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Abstract

Until recently historical reports concerning endometriosis begin with the 1860 publication by the pathologist Rokitansky when he described "benign sarcoma" describing three phenotypes in the uterus among some of the females of his many thousands of autopsies performed in Vienna. The defining of adenomyosis, then endometriosis improved with ensuing pathologists providing better descriptions brought about by the addition of improved microscopy for histological examinations introduced by Rudolf Virchow, Hans Chiari and Friederich von Recklinghausen, as well as advanced tissue specimen preparation, especially using the microtome with diamond cutting blades, used by William Welch, Robert Myer and Thomas Cullen at the Johns Hopkins Hospital in Baltimore, USA. So too did John Sampson continue with those advanced pathology methods when he moved from the former location to Albany in New York. Of all those revered professors, only Cullen and Sampson were physicians, actually highly capable surgeons with a strong interest in gynecology, and who focused their pathology reports on trying to explain the patient's symptomatology and correlate their live operative findings. Two recent authors have started the process of deciphering the past enabling one to track the disorder of endometriosis back to Egyptian times (1855 BC), thereafter to Hippocrates and his *histerikos-hysterike pnix* disorders and the idea of "suffocation/ strangulation of the womb". However, the association of severe abdomino-pelvic pain with menses appears to have taken centuries to clearly emerge. The preferred idea espoused by Plato, Pliny the Elder, Soranus, Celsus and a procession of physician philosophers through to both the early and late Middle Ages as well as the Renaissance, was that the symptoms which today we attribute to endometriosis were due to "suffocation/ strangulation of the womb". This diagnosis prevailed within Christian, Jewish and Muslim/ Zoroastrian/ Persian societies and was widely considered to be "due to remaining barren for too long after puberty". All the authorities noted that the symptoms, often described as "hysterical" and sometimes as "demonic possession" would disappear permanently after the woman "fulfilled her marital duties" and bore children. The nineteenth century was possibly a worse era for women with endometriosis with the popularisation of psycho-neurogenic ideas espoused by prominent physicians like Thomas Sydenham and practiced by "off-track" psychiatrists such as Sigmund Freud. It was Sampson who unraveled the complex pathogenesis of endometriosis and led to the improved outlook for women today.

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INTRODUCTION

Our current knowledge about endometriosis is derived from the work of John Sampson and his detailed publications covering two important theories/ mechanisms concerning its pathogenesis. John Sampson defined the term "endometriosis" in 1925 [1], and most gynecologists are familiar with his implantation theory (being secondary to a mechanism involving retrograde spill from the fallopian tubes) which he proposed in 1927 [2], and fully described in a lecture he presented to the American College of Obstetricians and Gynecologists in 1940. This lecture was in response to an invitation to explain the implantation theory and was published in the college journal following its presentation [3]. However, this mechanism cannot explain all forms of endometriosis hence many have proposed alternative pathogenetic mechanisms. Nonetheless, with an appreciation of Sampson's earlier studies on myomata and the venous drainage mechanism of the uterus [4,5], he was able to show that foreign material could escape from the uterine cavity and appear in the uterine veins [6]. This led him to publish his important first mechanism/ theory under the title of 'Metastatic or embolic endometriosis due to the menstrual dissemination of endometrial tissue into the venous circulation' in 1927 [7]. This was an earlier publication in 1927 from that reporting on the implantation theory.

PERSONAL PERSPECTIVE

Having graduated in medicine as an MD 50 years ago (1970), and specializing in Obstetrics and Gynaecology 6 years later, thereafter Subspecialty practice (Certification in Reproductive Endocrinology and Infertility; 1990) involving advanced

laparoscopic surgery and Infertility management 30 years ago, I have been perplexed that Sampson's work was not clearly presented. Younger trainees may still not be aware that John Sampson's work explains why normal menstruation is a controlled process, mainly on the basis of the unique vascular arrangement of the uterus, particularly that pertaining to the venous drainage [4]. Furthermore, the mechanism by which leiomyomata can cause menorrhagia is also based on disturbances of the venous drainage mechanism described by Sampson more than a century ago [8]. It is Sampson's work which explains why myomata in the periphery of the uterus can cause abnormal uterine bleeding and disturb fertility, contrary to current teaching that only intracavity and submucus fibroids are clinically relevant. My group has also attempted to redress current teachings with respect to endometriosis and adenomyosis [9], including that condition known as deeply invasive endometriosis (DIE) and specifically that of deeply invasive endometriosis involving the rectum (DIER) [10] from John Sampson's perspective. By understanding these processes, I believe we can reduce the burden of surgical treatments for young women and manage their endometriosis/ adenomyosis conditions by applying long-term hormonal suppression therapy [11].

SAMPSON'S POSITION IN THE EVOLUTION OF UNDERSTANDING ENDOMETRIOSIS

John Albertson Sampson (1873-1946), was born in Troy, New York and graduated MD at Johns Hopkins University in 1899. After completing his internship, he undertook a residency in gynecology under Dr Howard Kelly until 1904, following which he moved to Albany in New York establishing a private practice. In addition, he was attached to the Albany Medical College where, in 1911 he was appointed Professor of Gynecology. In 1927 he was also appointed Gynecologist-in-Chief at the Albany Medical Hospital thereafter spending his remaining career on the shared campus with the university college. At Johns Hopkins during the 4 years of his gynecological residency, Sampson had exposure to the lectures and advice of Thomas Cullen who was the Director of Gynecological Pathology from 1893. Sampson was also in the key position to discuss Kelly's operative specimens with Cullen, who was not only a pathologist, but an accomplished gynecological surgeon. Sampson published 18 articles, including book reviews, on surgical and gynecological subjects by the time he left Johns Hopkins at the end of 1904. These were mostly as sole author, none with Cullen as co-author. At Albany, Sampson remained a bachelor and worked tirelessly, completing many unique studies and achieved a total publication profile of 68 articles, each being extensively detailed in its descriptions and abundantly illustrated, mainly with his unique radiomicrographs for he was also a pioneer in this application of the new technology involving X-rays [11]. Sampson's final publication was in 1946, the year of his death following a motor vehicle accident, although, at age 73 years, he was still working until that event.

In drawing attention to Sampson's two theories/ mechanisms and his numerous articles, this infers he had a central position in clarifying the evolving understanding of the conditions embraced under the term "endometriosis". I personally believe this to be the correct view, but researchers will need to investigate a progressive line-up of historical figures who preceded Sampson and advanced their own unique contributions, each reflecting the limitations as well as the advances prevailing within their personal eras.

CARL VON ROKITANSKY, THE PATHOLOGIST AROUND WHOM ENDOMETRIOSIS PIVOTS, 1860

The historical background for the pathogenesis of endometriosis is usually cited as commencing with Carl von Rokitansky (1804-1878) who, at the second Medical School in Vienna provided the first descriptions of the two entities which later received their current titles - endometriosis and adenomyosis - in 1860. At that time Rokitansky was still continuing the tradition of bare-hand, naked-eye examinations as established by the acknowledged Founder of modern pathological anatomy Giovanni Battista Morgagni (1682-1771). These were macroscopic morbid pathology descriptions. By a state mandate of 1753, under Emperor Francis I Stefan ruling with the popular Habsburg Empress Maria Theresa, autopsies had to be carried out on all patients dying at the General Vienna Hospital, enabling Rokitansky to conduct more than thirty thousand, possibly sixty thousand post-mortems. He published his Handbook of Pathological Anatomy in three volumes across the years 1844-1846; a major treatise of macropathology. Following an academic visit to Paris in 1842, Rokitansky did introduce microscopy into his department, but he found it of limited value in the 1850's before adequate tissue preparation and staining techniques developed in Vienna. He did add microscopic histology into his 1860 "benign sarcoma" descriptions with three phenotypes noted containing endometrial stroma and glands:

i. *Sarcoma adenoids uterinum,* with invasion of the myometrium

ii. *Cystosarcoma adenoids uterinum*, the cystic variety, including a *polypus* variant

iii. *Ein ovarial-cystosarcom,* describing endometriosis within the ovary

These descriptions implied new diseases, but the reality is they are the first "modern" descriptions of conditions affecting the female "uterus" ("deep pelvic structures"), for at least 200 years prior [12]. At this stage the "sarcoma" entities were embraced as variants of the same process (categorized benign), and were seen to be distinct from both fibroids (benign), and carcinoma (malignant). It would await Sampson to clarify this terminology to what is understood today. Although Rokitansky's descriptions have been challenged, particularly by Robert Scully 1921-2012 Professor of Pathology at Harvard Medical School, who was dissatisfied with the *"polypus"* inclusion, there is wide acceptance that these descriptions by Rokitansky should be accepted as two of the three essential criteria, recently put forward by Benagiano and Brosens [13], are satisfied, albeit belatedly [14,15].

THOSE WHO INFLUENCE ROKITANSKY

Rokitansky's publication of 1860 constitutes an important event but was not a spontaneous epiphany. One needs to consider the interactive influences of a number of bio-scientific thinkers of the early nineteenth century including poet-scientist Johann Wolfgang von Goethe (1749-1832), who objectively and precisely

sketched plants and animals and coined the term 'morphology'. For it was he who influenced the brothers Alexander (1759-1859), and Wilhelm (1767-1835), von Humboldt who separated the Arts from Science and introduced deductive scientific thinking based upon research. So, too did von Goethe directly influence the young 'disciple' Johannes Peter Müller (1801-1858), who was called to the Chair in Anatomy and Physiology in Berlin in 1833, having already published work on the embryology of "his" Müllerian ducts, followed by his monumental Handbook of Human Physiology in 1840. Along with Alexander von Humboldt they, in turn, influenced Charles Robert Darwin (1809-1882), and promoted natural scientific thinking throughout the universities of Germany, including Vienna.

HISTORICAL NOTE CONCERNING THE POLITICAL GERMAN PERSPECTIVE

The region of Germania, comprising many tribes with a similar language structure, was a border region under the Roman Empire and thereafter the Germanic Territories were embraced within The Holy Roman Empire which began when Pope Leo III crowned the Frankish King Charlemagne as the first Carolingian Emperor in 800 AD. Regarding itself as independent from the Vatican and unofficially known as the Holy Roman Empire of the German Nation, it persisted until 1806 when it was dissolved by Napoleon. Following the Napoleonic Wars, resolutions at the Congress of Vienna in 1815 created the Empire of Austria and the German Confederation ruled under the Austrian presidency. Thereafter the Kingdom of Germany was established in 1871, arising from the Duchy of Prussia uniting with other Germanic states. This union excluded Austria with its capital, Vienna, and which continued under the Austro-Hungarian compromise of 1867 until 1918, when its numerous member nations sought their respective independent status at the Treaty of Versailles in 1919. The treaty specifically forbad any union between Austria and Germany.

RETURNING TO THE INFLUENCES FOR ROKITANSKY

Considered together, the aforementioned 'revolutionary' minds who embraced science, arts and philosophical ideas, influenced emergent embryologists such as Johannes Friederich Meckel (1781-1833), disciple of Jean-Baptiste Lamarck (1744-1829); also Casper Friederich Wolff (1733-1794), embryology founder and believer in epigenesis; and Karl Ernst von Baer (1792-1876), founding father of embryology and critic of Charles Darwin. Together they ushered in a period of scientific enlightenment. These are only a few of the medical scientists and thinkers who directly influenced Rokitansky's education.

The Second Vienna Medical School was established by Baron von Turkheim (1749-1824), who centered all teaching and research around Rokitansky's autopsy table leading to one of the most fruitful epochs in Viennese medicine. In 1838 Rokitansky described partial Müllerian agenesis, an anomaly which carried his eponym but would become known as the Mayer-Rokitansky-Küster-Hauser Syndrome paying homage to historical contributors. Professor Mayer of Bonn (1787-1865), Germany had reported a case of vaginal agenesis in 1829, hence the Rokitansky Syndrome gradually acquired the names of the several professors who had observed Müllerian disorders although it was Rokitansky who provided the full description.

Conversely with his reporting in 1860 of "benign sarcomas" (later to become known as adenomyosis by Cullen in publications of 1908, 1914 and 1920 [16-19], and endometriosis by Sampson in 1925 [1] these conditions were seen to be diseases of Müllerian excess. Given the subsequent disputes about pathogenesis, this view could be considered appropriately perceptive.

HISTORICAL BACKTRAIL

The historical back-trail for endometriosis (and its variant, adenomyosis) reveals that it did not emerge anew in the middle of the nineteenth century, but descriptions in various latin tomes 200 years earlier indicate the condition was not rare in post-pubertal women and the descriptions do not at that stage, claim the findings as novel [12]. The historical trail actually goes back much further with seminal reports best described by the Nezhat brothers, all Iranian-born gynecologists. In their comprehensive historical contribution [20] they made the perspicacious observation that *"to exclude the formative years leading up to the microscopic discovery of endometriosis is to deprive our discipline of an invaluable reservoir of knowledge that may reveal essential new insights about a disorder that continues to reign as one of gynecology's most perplexing diseases."* For the modern Evidence Based Medicine purist, the following ideas may not be universally accepted [15], but I, for one, like the story, which includes the idea that hysteria (ungovernable emotional excess), the now discredited disorder that the eminent Sigmund Freud (1856-1939), studied in large numbers of young women in the late nineteenth / early twentieth century, was most likely an endometriosis-triggered disorder. The Nehzat group raked through Oxford's Bodleian Library and discovered 13th-century manuscripts depicting imagery of a young woman doubled over in pain suffering "strangulation of the womb" a condition which can trace its derivation to the *hysterikos-hysterike pnix* disorders described by Hippocrates (460-370 BC), and other Greco-Roman authorities, which in turn was derived from the ancient Egyptians with similar documentation from 1855 BC. Of further interest it is apparent that such women actually suffered infertility, and that is why the uterus was "upset". This infertility was usually sheeted to the woman as representing her failure to be a good wife in her marriage and unsuited to motherhood. In the circumstance of achieving a normal pregnancy, the attending doctors invariably noted that her pelvic pain and associated symptoms became resolved and she would now be classified as a "normal, good woman". From the time of Hippocrates, physicians have urged women suffering from dysmenorrhoea to "marry and conceive as quickly as possible". Even Plato, who was not a physician, expressed his opinion (375 BC), that women with menses-related pain were suffering from "suffocation of the womb", due to remaining barren for too long after puberty. The Nehzat historical document indicates that many of history's revered writers added to the subject – including the Roman scholar Pliny the Elder (23-79 AD), and the Greek scholar Soranus of Ephesus (98-138 AD), who is known to have conducted autopsies. Soranus proposed inflammation as a cause of "suffocation of the womb". The Persian physician Hunayn Ibn-Ishaq al-'Ibadi (809-873 AD), endorsed the Hippocratic Corpus. The Roman encyclopedist

Aulus Cornelius Celsus (25 BC -50 AD), wrote *De Medicina*, the only surviving book of a series of encyclopedia. *De Medicina* itself is divided into eight books, book 3 pertaining to specific diseases. Celsus described the recurrent nature of attacks of uterine pain, sometimes with associated "hysterical fitting". The Greek physician Dioscorides (40-90 AD), who wrote the 5-volume *De Materia Medica*, which became the basis for medical teaching over the next 15 centuries, wrote about intermittent menses-related pelvic pain, sometimes with collapse, from "strangulation of the uterus". Greco-Roman Galen (126-210 AD), of Pergammon, now Bergamma in Turkey, became physician to several Roman Emperors. He developed unique anatomical drawings said to be derived from his well-known animal dissections (as autopsies were banned in Rome at the time). However, his description of swollen and inflamed uterine ligaments in women with uterine pain, implies that he was familiar with the utero-sacral ligaments, a common site for endometriosis; albeit Galen is known to have dissected Barbary macaque monkeys, a species of primate which is known to develop endometriosis, especially those which have no offspring. Galen also connected psychological disturbances of women to this disorder of pelvic pain from uterine suffocation/ strangulation.

A female physician from the early Middle ages Trota or Trotula of Salerno (1050-1097), wrote 3 books, comprising 200 manuscripts, on the conditions and treatments of women, collectively known as the Trotula. She was the first writer to attempt to correct misogynistic views about "the secrets of women", and described many of the mysterious actions, which earlier writers described as hysteria and anti-matrimonial behaviour, as foundered in the disorder of uterine suffocation/ strangulation being clearly a menstrual-related disturbance.

In the late Middle ages and early Renaissance period, Flemish anatomist and physician Andreas Vesalius (1514-1564), is regarded as the founder of modern human anatomy as he was allowed to conduct autopsies on human corpses, thanks to the Protestant Reformation movement. Vesalius became Professor of Surgery and Anatomy at the University of Padua (It: Pavia), in 1537. The Protestant Reformation movement was started by Martin Luther (1483-1546), who published his treatise comprising 95 theses from within the Holy Roman Empire (*of Germany*), and which was condemnatory of the Roman Papacy. Luther was particularly annoyed about the practice of "indulgences" which enabled wealthy sinners to be absolved by payment directly to the Pope. Luther's treatise led to Pope Leo X issuing a Papal Bull in 1520 termed *Exsurge Domine* which required the "heretic priest" to retract his 95 theses. Luther famously refused and was excommunicated by the Roman Vatican the following year thereafter setting about the creation of his new Protestant Church. This entailed rejecting Roman Catholic views about the Soul which was the foundation for Vatican's view against autopsies. Apart from a requirement for respectful handling, autopsies are not banned in the Protestant view. Hence, Vesalius did not encounter opposition to his dissections performed in Switzerland and other Reformist countries enabling him to publish his groundbreaking work "*De Humani Corporis Fabrica Libri Septem"* (On the fabric of the human body) in 1543. However, it appears the Vatican was not so tolerant and Vesalius appears to have been pursued by the Inquisition in some Italian and Spanish jurisdictions. With respect to his dissections on the female reproductive system, Vesalius corrected Galen's descriptions of the 2-chambered uterus, but appears to have had few female, especially pregnant, cadavers available for dissection. Possibly he was not very interested as it was his follower in 1551 to the Professorial Chair of Surgery and Anatomy in Padua, Gabrielle Fallopius (1523-1562), who described the Fallopian tubes. Despite their enormous contributions to human anatomy however, neither Vesalius nor Fallopius made any relevant advanced contributions to the subject of "suffocation/ strangulation" of the uterus. In fact, the one case, in Spain, where Vesalius was to undertake an autopsy on a woman following a seizure due to suffocation/ strangulation of the uterus, she awoke during her autopsy. Although not clearly substantiated, Vesalius was pursued by the Inquisition and it was during his escape he met an early accidental death.

The research undertaken by the Nehzat brothers indicates that prominent medical authorities of the 16th Century accepted the diagnosis of suffocation/ strangulation of the womb in explaining women's unique illnesses but one, French barber-surgeon Ambroise Paré (1509-1590), clearly related the disturbances to menstruation and described "swollen uterus" and "distensions on the uterine ligaments" as features of the condition. Unfortunately, however, the process of enlightenment arising from the Renaissance was slow to dismiss the primitive thinking of the Middle Ages which categorized many women with the symptoms of uterine suffocation/ strangulation as having demonic possession or being immersed in witchcraft. Such women were often blamed as causing unexplained community ailments including delivering the plague. Even the esteemed William Harvey (1578-1657), wrote that female hysteria was brought on by "unhealthy menstrual discharge" related to "being too long unwedded". From a scientific perspective Harvey did make one small positive contribution in demonstrating that he could reproduce the woman's hysterical symptoms by distending her uterus (during treatment for cervical ulceration).

However, despite the terrible consequences for women with uterine suffocation/ strangulation in the Middle Ages, the next period, one of scientific and artistic enlightenment was characterised by the evolution of neuroscience. This period led to a shift in focus away from the uterus as the cause for female hysteria but considered it more likely an expression of the increasingly popular psychological-neurologenic theory. Despite embodying some of the best attributes of the scientific enlightenment period, revered physician Thomas Sydenham (1624-1689) described that female hysteria was *a "disease of civilization, more common in leisured ladies with lives characterized by idleness and overindulgence"*; hence he thought it was caused by *"frayed nerves"*. For the next 200 years, many prominent physicians including Sigmund Freud (who was mentioned at the start of this section) identified hysterical behavior including nymphomania and neuroses as having an entirely psycho-neurogenic basis, totally removed from any pelvic connection.

The beginnings of modern thinking regarding endometriosis and adenomyosis can be ascribed to German physician Daniel Shrön (Shroen; 1690), who described ulcers/ deposits scattered throughout the visceral and peritoneal surfaces of

the abdomen and pelvis; probably the first proper description of endometriosis [12,20]. However, a contemporary, Dutch anatomist Frederik Ruysch (1638-1731), later provided even more detailed descriptions of widespread peritoneal lesions, which he suggested was most likely a consequence of menstrual blood forced backwoods following obstruction to normal flow, an idea that Sampson was reluctant to entertain until 1927 [2]. Ruysch linked these findings to the woman's history of cyclical abdomino-pelvic pain. The next stage in clarifying the pathology underlying these symptoms was developed by the French pathologists who took the art of autopsy investigations to an advanced level, particularly heralding the application of histology pioneered by Marie François Xavier Bichat (1771-1802). It was the French group, including Armand Trousseau (1801-1867), and Alfred Velpeau (1795-1867), who changed the thinking from suffocation/ strangulation of the uterus to a new set of terms – catamenial hematoceles, pelvic sanguinous tumours and sanguinous cysts. This enabled advanced clinicians to dismiss the "hysteria" label and deal with their female patients from a clear pathological entity. Even Rokitansky admits his ideas which led to the first clear depictions of uterine adenomyosis, emerged after his important visit to the French pathologists in 1842, following which he added the histological findings into his autopsy evaluations. So too, did Sampson apply terms such as "heterotopic endometrial tissue" until firming his definition of endometriosis in 1925 [1].

RUDOLF VIRCHOW

After Rokitansky's important publication of 1860, the evolution towards Sampson considers other German pathologists, each stepping up on the foundations laid by their predecessor [21]. Although not directly interested in pelvic disorders of the female, Virchow is an important pillar in the evolution of histopathology. Rudolf Ludwig Carl Virchow (1821-1902), studied in the University of Berlin where he projected the new ideas of cell biology and cell theory. Microscopy was an essential tool enabling him to extend on the unique cellular theories of his mentor Johannes Müller (1801-1858), previously mentioned with Rokitansky, and his assistant Theodor Schwann (1810-1882), who had published his foundational *Microscopical Researches into the Accordance in the Structure and Growth of Animals and Plants* in 1839. From this Virchow developed his revolutionary cell theory formulated as *omnis cellula a cellula* (all cells from other cells) and his treatise entitled *Cellularpathologie* published in 1858). This idea gained immediate recognition and enabled Virchow to demote other theories of disease causation, including Rokitansky's blastema theory which was based on the long-standing idea of haemato-humoral pathogenesis. Even Rokitansky soon acknowledged that Virchow's cellular origin of disease was the better path, stating in 1855 that he *"encouraged Virchow to further develop this natural scientific conception of disease".* Rudolf Virchow is universally acknowledged as the "Father of Modern Pathology" as well as "Founder of Social Medicine" and casually regarded as the "Pope of Medicine". These terms reflect a varied, erudite and colourful political history which is exciting to read about, and is one entirely missing from the medical landscape of today.

FRIEDERICH VON RECKLINGHAUSEN

Friedrich Daniel von Recklinghausen (1833-1910), had been the first assistant of the famed Rudolf Virchow who, in Berlin, introduced advanced microscopic descriptions to all the organ pathologies of the body. With advancing methods of preparation of thin tissue slices, Von Recklinghausen became the acknowledge "Father of Modern Pathology". He described the microscopic appearances of adenomyomata in a brief report in 1893 and an extensive treatise in 1896. He then established a Chair in Strasbourg (the city of Alsace-Lorraine on the French-German border), at the time, following the Franco-Prussian War, a German City (1871-1918), but nowadays French, apart from a short period as German again, under Nazi occupation 1940-1944. Following his mentor, Virchow's demotion of the inflammatory theory proposed by Rokitansky for his 1860 findings, von Reklinghausen developed his ideas that the adenomyomata were derived from embryological rests of the resorbed Wolffian Duct. He published these ideas in 2 short articles in 1893 and 1895 in which he referred to Rokitansky and his theories, preferring his own. Reklinghausen described microscopic pseudoglomeruli that resembled the glomeruli of the kidneys and which thus formed the basis for his Wolffian rest theory. Von Reklinghausen also included the recently described "*salpingitis isthmica nodosa"* as a form of his "adenomyomata" and similarly, he felt, was derived from Wolffian rests. It was Hans Chiari (1851-1916), assistant of Rokitansky, who described, among other important pathologies) the condition of "*salpingitis isthmica nodosa*" in 1887. As von Reklinghausen had a formidable reputation in histopathology, Chiari, who believed his eponymous condition had an inflammation basis (like Rokitansky's adenomyomata), allowed the Wolffian cell-rest hypothesis to prevail. However, it was the first gynecological pathologist in North America, Thomas Cullen, who demonstrated that neither the inflammation nor the Wolffian theory was correct, but these lesions were clearly derived from the Müllerian tract. This became a concept to which von Reklinghausen conceded in 1903 after 2 of his own students, namely William Henry Welch (1850-1934), and Robert Meyer (1864-1937), showed him the indisputable evidence which Cullen had revealed in his exquisitely mounted, and clearly superior, histological specimens.

THOMAS CULLEN

Thomas Stephen Cullen (1868-1953), graduated in Medicine in Toronto, Canada in 1890, thereafter training as a Gynecologist at the Johns Hopkins University 1891, but also spending 6-months working with Pathologist Johannes Orth (1847-1902), in Gottingen, Germany before returning to Johns Hopkins in 1893. Ort was another protégé of Virchow and actually assumed his mentor's Chair in Pathology at Berlin on Virchow's retirement. However, the senior surgical position Cullen had expected with Howard Kelly was deferred hence he established, at Kelly's invitation, a pathology laboratory, becoming the first Gynecological Pathologist in North America whilst also practicing as a gynaecologist in private practice and assisting Kelly with his gynaecological operations. Cullen eventually gained the position as Head of Gynecology in 1919 after the retirement of Kelly

and had the title of Professor of Clinical Gynecology, a position he held until retirement in 1939. Between 1894 and 1909, Cullen wrote 4 books on gynaecological diseases which married histopathology with clinical symptoms and signs, one of which was Adenomyoma of the Uterus [16]. Subsequently he published on the specific subject of adenomyosis of the rectovaginal septum [17,18] as well as an accumulated experience of his findings of extra-uterine adenomyosis, detailing 10 sites which he had personally documented [19]. However, the worst cases were those involving the recto-vaginal septum, numbering 19 in total, and which led to its eponymous title "Cullen's Disease". Cullen also published on uterine haemorrhage and its treatment [22], classifying these into pregnancy-related and non-pregnancy related. His description of discoloration of the skin about the umbilicus [23,24], became known as Cullen's sign, particularly when related to ectopic pregnancy, about which Cullen wrote extensively.

In the previous section I described Cullen's successful work to indicate that adenomyosis had its pathogenesis derived from Müllerian origins, rather than from cellular rests of Wolffian duct origin. This meant Cullen taking on the eminent figure of Friederick von Reklinghausen, a giant in his time who, having studied under Rudolf Virchow, progressed histopathology with improved tissue preparations, their embedding and staining, along with the skillful process of cutting very thin tissue slices and applying improved compound microscopy. Much of these advances were derived from Professor of Physiology, Jan Evangelista Purkynē (Purkinje) (1787-1869), from the Austro-Hungarian region of Bohemia (now Czech Republic). His name is attached to his discovery of large multi-dendritic neurons in the cerebellum, pigmented neurons in the Substantia Nigra and the fibres conducting electrical impulses from the atrio-ventricular node in the heart. Along with creating improvements in compound microscopy, Purkinje developed the first microtome to create very thin histological specimens, an instrument probably not used by von Reklinghausen in Strassburg but rapidly adopted by his assistants such as William Welch and Robert Myer when they worked in independent locations. When Cullen returned to Johns Hopkins from his European sojourn in 1893, he worked in the pathology laboratory of William Welch who had been an assistant under von Reklinghausen. Cullen assisted the surgical procedures of Howard Kelly as well as undertaking the pathology evaluation of Kelly's specimens with Welch. When Cullen read von Reklinghausen's monograph of uterine and tubal adenomyomas, he had "an epiphany" and pulled out his own histology slides on similar cases undertaken in Baltimore during 1894 and 1895. Cullen's histological specimens, confirmed by William Welch and later by Robert Meyer showed clearly that the adenomatous lesions were derived from Müllerian tissue and not derived, in any way, from Wolffian rests. This finding related to improved tissue specimen preparation using a modern American-made microtome utilizing a diamond cutting blade, mounting his specimens in celloidin as well as utilizing the latest German-made microscopes which had been installed in the Pathology laboratories at Johns Hopkins. Cullen was able to take thick specimens of uterine tissue and cut ultrafine slices which could be examined sequentially, enabling a continuous tracking of adenomyoma tissue from the periphery of the uterus back to the uterine cavity. This detail concerning Cullen's tissue preparation is best described by Ronald Batt in Chapter 4 of his History of Endometriosis [21], which is titled "From von Rokitansky to von Reklinghausen to Cullen" [25]. Although Cullen visited von Reklinghausen in 1896 to discuss their different findings regarding adenomas of the uterus, it was not until 1903 after presentations by his former students Welch and Meyer, that von Reklinghausen finally acceded that the pathogenesis was clearly Mullerian-derived and the Wolffian hypothesis was discarded. Although von Reklinghausen did not accept giving Cullen, whom he saw as not having proper training as a Pathologist, face-to-face credit, he confided in colleagues the viewpoint that his autopsy specimens, "hand-cut with a razor and mounted in amyloid liver" were different, (meaning inferior to), those of Cullen's fresh surgical specimens.

To understand the man, Cullen, this is best revealed in his "Address in Gynaecology" [26], where he was invited to speak to the Canadian Medical Association in London, Ontario. The first half of his presentation dealt with Cancer where he presented details from many areas of the body; particularly that of breast cancer, skin cancer, cancer of the lip, cancer of the tongue, cancer of the stomach, cancer of the intestine, cancer of the rectum and gynecological cancers, particularly of the uterus, the endometrium, the cervix and the ovaries. He made strong observations about the need for surgery to be conducted in the early course of those disease processes, and he was particularly critical of those surgeons who did not *"dissect fully and excise widely"*. A telling comment, with historical interest is his statement:

"When I started medicine a quarter of a century ago, asepsis was slowly creeping into Ontario, and Lister's carbolic spray was still in vogue. We examined very little operative material microscopically in those days. The time is rapidly drawing near when every surgeon, before he becomes a real surgeon, must have a thorough grounding in surgical pathology as he now has in the principles of bacteriology."

The second half of Cullen's presentation focused on myomata and adenomyomata of the uterus; along with that specific condition of "adenomyosis invading the rectovaginal septum" on which he soon published specifically the following year [17]. He described the details of a 37 year old woman admitted to the Johns Hopkins Hospital on June 4th, 1913; she had previously had a supravaginal hysterectomy with bilateral salpingo-oophorectomy, undertaken for pelvic pain in San Francisco but her symptoms persisted along with irregular, almost continuous bleeding from her remaining cervix. Cullen operated and reported:

"We are here dealing with an adenomyoma which has formed a cystic mass in the left broad ligament and which has become densely adherent to the rectum. We found the rectum densely adherent to the bladder, and the left broad ligament was filled out by a rather cystic growth. Those assisting at the operation thought that we were dealing with a malignant growth which had spread into the broad ligament." Cullen completed a conservative operation for what is now termed deeply invasive endometriosis involving the rectum (DIER), leaving a portion of the "now termed endometriosis/ adenomyosis" attached to the rectum. When Cullen later examined the excised tissues he reported:

"on microscopic examination it was found that the wall of the blood stained cyst was lined by one layer of cylindrical epithelium, and that this rested on a definite stroma consisting of cells having oval vesicular nuclei. The more solid portions of the groeth were made up of non-striated muscle fibres arranged in whorls, and of quantities of uterine glands embedded in their characteristic stroma. In some places only two or three glands with the surrounding stroma were visible but at other points miniature uterine cavities were found."

Cullen was planning further surgery for the woman to fully *"shell out the thickening in the right broad ligament, remove the cervix and then a portion of the rectum to which the growth is intimately blended. Unfortunately, the woman became weaker in the post-operative period and died June 19th."*

With respect to the specific surgical procedure for DIER, Cullen later stated *"The removal of an extensive adenomyoma of the rectovaginal septum is infinitely more difficult than a hysterectomy for carcinoma of the cervix"*. In tackling this disease Cullen believed that Gynaecologists should be trained as fully competent abdominal surgeons. He stated: *"Where the lumen of the bowel is greatly narrowed, a complete segment of the rectum should be removed with the uterus, and an anastomosis should be made." In such cases "surgeons should perform a "preliminary permanent colostomy... later the pelvic structures can be removed en bloc" [17, 18].*

However, despite Cullen's anatomical knowledge and surgical expertise, especially that involving bowel anastomoses, he described some unpleasant complications which included vesicovaginal and rectovaginal fistulas. In this pre-antibiotic era, despite the advanced sterile surgical techniques practiced at the Johns Hopkins Hospital, most of the women who had complications died, like the one reported in London, Ontario in 1913.

This subject of DIER and its surgical management, has recently been analysed [27,10] and it is relevant for this presentation to know that Sampson had quite different views about managing this condition albeit that both men were extremely competent as abdominal and pelvic surgeons and had exquisitely intimate knowledge about the pathology as well as the pathogenesis of this subject. Both Cullen and Sampson wrote about the appropriate surgical management of rectovaginal endometriosis, one promoting aggressive surgery, the other indicating a more conservative management was better; this debate, started more than 100 years ago, still continues today [10], but should not if due attention is paid to the publications of John Albertson Sampson.

CONCLUSION

This historical article is intended to cement the place of Sampson into its appropriate position as the exceptional Physician who truly understood the pathogenesis, the pathology and the clinical manifestations of the perplexing disease of endometriosis. He was the right person, at the right historical moment to achieve this wisdom, coming off the sequential work of a number of giants in the world of Pathology and his contemporary clinical colleagues in the North America. This article is intended to dove-tail with its sister article entitled Understanding Endometriosis which specifically details Sampson's contribution to explaining endometriosis in its 8 different clinical scenarios, 4 being common and 4 being uncommon [11]. The article also supports the recent publications which reveal that women have historically been unfavourably depicted from Hippocratic, probably even earlier Egyptian, times with the condition of "hysteria" caused by suffocation/ strangulation of the uterus. Sampson has placed all this on a firm diagnostic footing which enables modern doctors to treat the condition of endometriosis in a rational and therapeutically valid manner.

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