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The past teaches

About the Cover

The Venetian Cardinal Domenico Grimani (1461-1523) purchased a 1,670 page Flemish breviary, possibly by Alexander and Simon Bening of Bruges, for 500 ducats (about $50,000 in 2022 USD) in 1520. The magnificent manuscript, known as the *Breviario Grimani*, contains psalms, hymns, texts, prayers for the hours of the day, and ornate calendars for each month. The month of February in the *Grimani* depicts a farm scene covered in snow, sheep in their stall, and a few barnyard animals searching for winter morsels. A peasant family (inset, left) appears to be taking comfort by an indoor fire. The covered chariot of Helios drifts across the night sky led by winged horses. Shortly after the breviary arrived in Venice, the art historian Marantonio Michiel marveled at the work's realism. "(Especially) laudable", he wrote, "are the calendar illuminations of the twelve months and, most remarkably, the one of February, where is child is visible peeing in the snow, and the pee is yellow against all the white, snowy and frozen countryside." Given the allegorical context of nearly all the works of art in these treasures, it is unclear what the artists are trying to convey with the young figure. The *Grimani* "February" is very similar to the "February" attributed to Paul Limbourg (fl. 1384-1416) in *Tres Riches Heures du Doc de Berry,* an earlier illmuniated breviary (c. 1412-1416) with a nearly identical farm scene, winter work, and a resting family. Perhaps the Benings of Bruges were paying homage to the Limbourg masterwork and the small inset of the urinating lad is a harmless bit of irreverance to lighten the long months of winter. The full image of the *Grimani* "February" thus graces this, the winter issue of the Journal, to seasonally illustrate the rich source of urologic history, both overt and sometimes hidden, that has been preserved for time immemorial by geniuses of the past.

Image Source: Biblioteca Nazionale Marciana, Venice, Italy, ms. Lat I 99 = 2138

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Editorial Office: 40 Sunshine Cottage, 19 Skyline Drive, Suite 1S B45, Valhalla, NY 10595.
E-Correspondence: editor@ijuh.org

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Foreward

W. Gilmore Simms, the preeminent early-19th century American scholar of art and literature, grappled with the cultural identity of the United States, noting that the coutnry "sprang into birth, fully grown, if not in panoply".(1) Compared to its European cousins, the new nation did not have centuries of literary tradition, of art, or of music that could provide ample material for fellow historians. In addition to major politicians, treaties, and books, Simms wrote, historians needed to look for the littler things, the more obscure features of society and of the humanities to develop a fuller picture of what America would become. "What portion of our history remains unwritten?" the professor asked. "What portion of it is so obscure that all may not equally see?"(1)

Urologic history is rich and deep but there are treasures to be found in the seemingly obscure, in the urologic record that has yet to be written. How that data is acquired is the hallmark of scholarship. Luckily, a tremendous amount of historical materials can be accessed through online portals. PubMed (1986) and Googlescholar (2004) remain the most popular search engines for contemporary medical literature but GoogleBooks (2005) provides a nearly unprecedented access to entire often historical books. With digital scanners churning along at rates of 1000 pages/hour, GoogleBooks has created a fully-searchable database of more than 5 million volumes. Another whole document archive, Hathitrust (2008) (hathitrust.org) was created to provide unrivaled access to over 17 million digitized items including archives of medical groups, physicians, hospitals, and federal and state governments. Many Hathitrust searches will also extend into the digital items of the Internet Archive (1996) (archive.org), which is also a trove of archived music and film. For full text searches of even older books, the Gutenberg Project (www.gutenberg.org) provides free access to over 60,000 volumes. The United States National Archives (www.archives.gov) and the Library of Congress (www.loc.gov) may have user-friendly search options, but their archivists and librarians are even friendlier. The French national library, whose archive of digitized medical and surgical prints are unheralded, may be accessed in English at gallica.bnf.fr. The German link to their national archives can be found at Deutschland.de/en. With a well thought-out research inquiry, these professional archivists are eminently helpful in finding an unopened folder, box, or container in their collection that might just align perfectly with a researcher's interest. Ancestry.com may be useful to find out if you are as French or German as you thought you were but may also provide access to birth, death, and immigration records or newspaper archives of persons whose urologic biographies may be sadly devoid of such information.

Urologists themselves have long been their own archivists and it was Felix Guyon, the father of French Urology, who was the first to start a urologic museum in 1900's Paris. To continue that heritage of study, the American Urologic Association supports the William Didusch History Museum at the AUA headquarters in Linthicum, Md. Every urologist, and certainly everyone interested in history, should visit the fine collection in Linthicum in person or, if unable, tour the virtualmuseum at urologichistory.museum.

The four papers (and one bio-snippet on Dr. Robert Proust) in this month's journal feature all of the above datasources, and more, which may provide readers new platforms to continue their own research.

We should echo Professor Simms in thinking what portion of urologic history remains unwritten merely because it was obscure and unknown. With such modern tools at our disposable, we can look forward to a rich future of history.

John L. Phillips, Editor

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Adrenaline Rush: the Race for the Crystallization of Adrenal Extracts by J Takamine and K Uenaka

Tetsumori Yamashima[1,*], Evan Spencer[2], John L. Phillips[2]

From the (1) Department of Psychiatry and Behavioral Science, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan amd (2) Department of Urology, New York Medical College, Valhalla, NY, USA.

**Correspondence: Tetsumori Yamashima, Takara-machi 13-1, Kanazawa, 920-8041 Japan; e-mail: yamashima215@gmail.com*

Introduction: The adrenal gland was first described by Eustachio in 1564, but its physiologic role remained unknown for three centuries. In the late 1890's, many researchers had directed their attention to the isolation of adrenal extracts, but all failed until the successful efforts of biochemists Jokichi Takamine and Keizo Uenaka. Takamine's patents on Adrenalin were the first ever awarded for a hormone and he used his royalties to improve international relations between America and Japan. There is considerable controversy, however, in how adrenaline was first crystallized, where the work was done, and to whom the credit for its discovery is given.

Sources and Methods: Published contemporary medical literature, newspaper archives, and publicly accessible research archives in Japan, Sweden, and the United States.

Results: Takamine was a multilingual businessman with a background in Western and Eastern medicine, a successful biochemist, and importer/exporter before he took on the project of isolating adrenaline. His successful patents and savvy business acumen allowed him to support innovative research in physiology. He hired Keizo Uenaka, who had experience with isolating ephedrine, to develop the critical methods required to crystallize adrenal extracts where other contemporaries, including Takamine, had failed. Takamine applied for and was awarded five immediate US patents for the discovery although he did not include Uenaka in that effort. Takamine co-founded the Nippon Club and the Japanese Society of New York, both of which ultimately survived the anti-Japanese fervor of the 1940's and, in 1912, worked to bring the gift of 3,000 Japanese cherry trees to Washington, D,C. The Japanese Patent Office honored Takamine as one of Japan's 10 Great Inventors but it was only after Uenaka's death in 1960, and the discovery of his laboratory manuals, was Uenaka's full role in the discovery of adrenaline made known.

Conclusions: Jokichi Takamine was an international benefactor and biochemist extraordinaire who, with Keizo Uenaka, was the first to crystallize adrenal medullary catechols. Takamine's efforts saved lives and did much to engender a spirit of Japanese-American goodwill that persisted for decades.

Keywords: Adrenal, Takamine, Uenaka, Discovery

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At the 52nd annual meeting of the American Medical Association in 1901, Jokichi Takamine (1854-1922), a Japanese-American biochemist and industrial leader, delivered a memorial lecture entitled 'The blood-pressure raising principle of the suprarenal gland' in which he said,
"*I am pleased to announce that I have succeeded in isolating the active principle of the gland in a stable, pure, crystalline basic form. .... I have termed the active principle of the gland as I have isolated it, 'adrenalin' .... and is over one thousand times stronger than the fresh glands.*"(1) Takamine and his young associate, Keizo Uenaka (sometimes written in English as Wooyenaka), crystallized adrenaline (or 'epinephrine' in the United States) in the summer of 1900, the first hormone ever to be isolated in the twentieth century from animal adrenal tissue. The compound transformed surgery, where it was used very soon thereafter in an attempt to control hemorrhage, the world's first effective asthma medicine, a remedy for anaphylactic shock, and, at least in one pugilist, for ringside boxing injuries.(2) Takamine moved from Japan to the United States to establish a research laboratory in Peoria, Illinois, where he worked to apply a traditional Japanese fermentation technology of sake, based on the aspergillus mold of *'koji'*, to Western whisky production, which had been based on 'malt'. In 1894, he filed the first patent in the US on a fungal amylase he isolated called Taka-diastase

critical to a more efficient alcohol distillation but which was more successfully marketed as an aid for dyspepsia. Supported by the pharmaceutical company Parke, Davis & Co., which purchased the rights to Taka-diastase, Takamine then moved to New York to establish his own laboratory, hired Uenaka, and where they ultimately crystallized adrenal gland extracts. Both 'Taka-diastase' and 'Adrenalin(e)' were ground-breaking innovations and contributed to establishing Takamine's reputation as a leading biochemist in the explosive progress of the early pharmaceutical industry in the twentieth century. This paper aims to better elucidate Takamine and Uenaka's route to the discovery of adrenaline crystals, its controversies, and its impact on the development of the modern pharmaceutical industry.

SOURCES AND METHODS

A literature review was conducted using the MEDLINE/PubMed database, the HathiTrust digital library (www.hathitrust.org), and the digital storage site of JSTORG (www.jstor.org) of primary or secondary source materials as cited. United States Patent Office records were searched through the www.uspto.gov portal. Records of Nobel Prize Committee decisions was accessed through the nomination archive at the nobelprize.org/nomination portal. New York Public Library holdings were searched using the photodatabase at oldnyc.org.

RESULTS

Anatomic Studies

The discovery of the adrenal gland itself is generally credited to Eustachi Bartolomeo Eustachio (c.1500-10-1574) who described the vascular connections of the right and left adrenal in 1564.(3) He described the adrenal as an accessory kidney or '*glandulae renibus incumbentes*' and it was not until 1656 when Thomas Wharton (1614-1673) proposed their neuroendocrine function.(3) Thomas Addison (1793-1860) famously noted the stigmata of the disease that bears his name in his landmark 1855 manuscript whereby both adrenal glands are affected by tuberculosis.(4) Albert von Koelliker, in 1852, using an improved compound microscope, was the first to appreciate the distinction between the adrenal cortex and medulla.(5) The great French physiologist Edmé Félix Alfred Vulpian (1826–1887) demonstrated in 1856 that ferric chloride would not only stain the medulla sea-green but that blood from the adrenal veins provided the same reaction while blood from other organs did not.(6) It was C. F. W. Krunkenberg who first surmised that the 'Vulpian' color reaction of adrenal extracts was similar to that of a common molecule in plants, a pyrocatechol, and that the adrenal medulla must be a source of other catechols.(7) Based on Addison's paper, and Vulpian's findings, there was now great interest that the adrenal cortex and medulla had different effects. Charles-Édouard

Figure 1. (Left) Jokichi Takamine (1854-1922), already a wealthy import/exporter in the fertilizer business and had patented the pharmaceutical Taka-diastase before tackling the challenge of the adrenal gland. (Right) Keizo Uenaka (1876-1960), the biochemist, hired by Takamine to come to New York and whose diligent efforts led to the first crystallized products of the adrenal gland. (Public domain)

Brown-Séquard (1817-1894) performed bilateral adrenalectomies in some 60 laboratory animals of different species.(8) None survived and he concluded that adrenal glands maintained a critical role in life by secreting substances into the bloodstream. Thus, by the end of the 19th century, a basic anatomy, histology, and embryology of the adrenal glands was appreciated; their function was not.

Physiologic Studies

The credit for the first demonstration of the effects of adrenaline is given to George Oliver (1841-1915) and Edward A. Schäfer (1850-1935). Oliver had originally detected a change in radial artery caliber in his adult son who had volunteered to eat extracts of ovine and bovine adrenal extracts from the local abattoir. Oliver journeyed to London in 1893 and worked with Shäffer who himself was engaged in blood pressure research. The adrenal extracts produced a transient hypertension in a dog that was so potent that the mercury column in the manometer almost overflowed.(9) The Oliver-Schäfer observations, published in 1895, heralded the first demonstration of the physiologic effects of the adrenal medulla and is regarded as a breakthrough in modern physiology and endocrinology.(10)

The Quest for Purification.

The effects of adrenal extracts on blood pressure proved to be transient physiologically. The active compounds responsible for such effects proved to be biochemically elusive as well. Otto Von Fürth (1867-1938), Benjamin Moore (1867-1922), and Felix Fränkel were all early physiologists who used basic chemical steps to try and precipitate the active hypertensive agent from adrenal extracts. Fränkel noted that the molecule of interest was a substituted catecol, as Kruckenberg had suggested, and that it was probably a derivative of a larger benzoyl molecule.(11) John J Abel (1857-1938), already famous as Professor of Pharmacology at Johns Hopkins, seized upon Fränkel's hypothesis, and focused on benzoylation procedures in hopes of purifying the active agent of the adrenal medulla. With Albert Crawford, Abel developed a pioneering but complex procedure incorporating benzoyl chloride which yielded a mono-benzoyl crystal he later termed epinephrine-hydrate.(12, 13) The extract could raise blood pressure and he was able to calculate the empirical formula for the compound he obtained as $C_{17}H_{15}NO_4$ but the derived substance proved less active than crude extracts themselves. The benzoyl process was troublesome for others as well and some, like Fürth, claimed that the 'epinephrine' Abel obtained was not pure, that Abel had obtained an inactive foreign substance, a benzoyl derivative of a

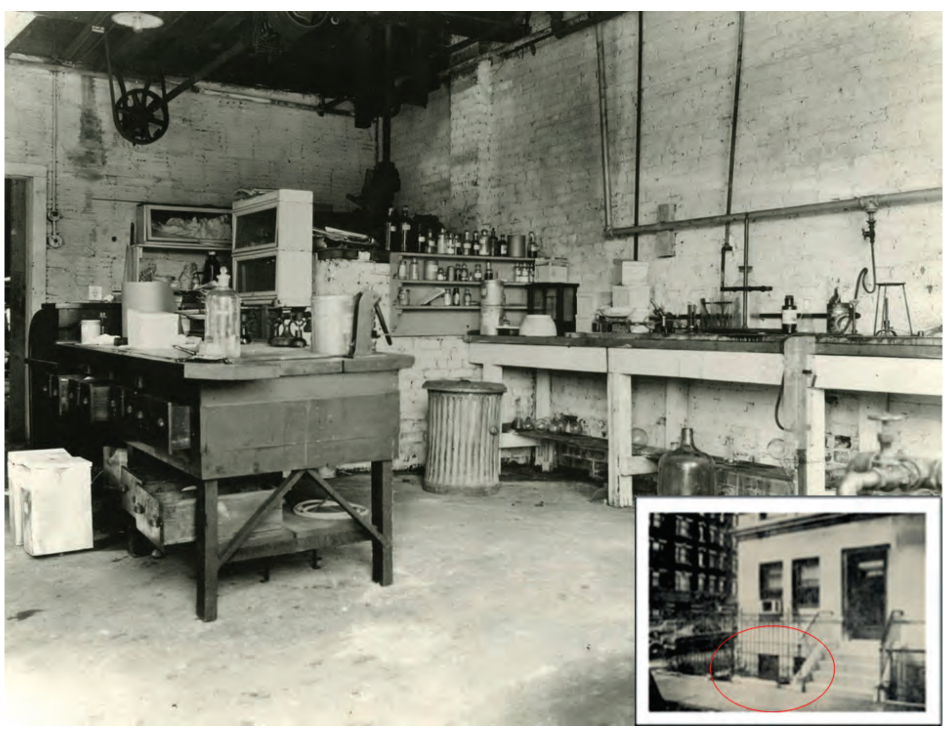

Figure 2. The Takamine Lab. Takamine in 1898 toiled here in a 109th street New York basement lab (see inset) from 1898-1900. He then brought in Uenaka who, within months, elicited a positive Vulpian reaction in a batch of crystals derived from kilograms of adrenal tissue, crystals which eventually yielded the drug Adrenalin and hailed as a modern wonder. (Public domain)

Figure 3. (Left) View of purported Takamine Lab in basement of this 4-story block on northwest corner of East 109th street, New York, NY (Japanese Heritage Foundation) (Right) 1912 view of a building with similar features including the Italienate cornice dentil mouldings prevalent in 19th century Manhattan. (New York Public LIbrary)

compound that had withstood the harsh requirements of a hydrolysis procedure in an autoclave. "The dispute between these two authors," Takamine wrote, "was not altogether amicably solved."(1) Abel himself later termed these struggles as "blunders of a pioneer" but did, as Takamine later wrote, "no doubt thrown some light on the chemical side. Unfortunately, he was not working with the active principle but a somewhat modified substance or the benzoyl-compound: and that these substances were "not crystallizable".(14, 15)

Takamine and Uenaka

Jokichi Takamine was originally from Kanazawa and after graduation from Kobu University, was sent on a scholarship to Great Britain where he mastered industrial chemistry. He returned to Japan and, in the Ministry of Agriculture, worked tirelessly to apply modern science and technology to traditional practices. He served as Chief of the Japanese Patent Office and learned early the important relationships between scientific discovery and business. He represented Japan at the World Cotton Convention where he met the New Orleans debutante Caroline Hitch in 1884 and, after their 1887 marriage, the couple lived in Japan for some years while he developed a successful US-Japanese fertilizer business.(16) At the same time, he discovered the enzyme *Taka-diastase*, an amylase in an aspergillus mold of rice, or '*koji*', the active ingredient required to make sake. He found that when applied to the American distillation practice in place of malt, koji could increase the yield and decrease the cost of whiskey production. The couple moved to Chicago to continue his work. Mrs. Takamine, who had campaigned to market her husband and his patents in the US, got a Chicago distillery interested in koji but initial profits were modest. At the same time, Takamine also noticed that Taka-diastase was useful for the treatment of dyspepsia. He himself benefited from the supplement as a sufferer and successfully sold the now patented enzyme to the Detroit-based pharmaceutical company Parke, Davis & Co.(17,18) The product was successful and, with his fertilization business, Takamine enjoyed substantive wealth. Meanwhile, Parke, Davis's general manager, William Warren, was intrigued by the blood pressure raising properties of animal adrenal tissues and, in 1897, asked Takamine to study in detail the papers of Moore, Fürth, and Abel. Now financially able to do so, Takamine moved his wife and two sons to 475 Central Park West, New York City and started his own lab in a 15 m^2 semi-underground room at East 109th street where he immersed himself for nearly 2 years in toil.(18) He floundered in perfecting the process of isolating anything active from large volumes of adrenal tissues. He therefore contacted the revered head of the Tokyo Imperial University, Professor Nagayoshi Nagai, with whom Takamine had earlier co-founded the Tokyo Chemical Society and who, in 1885, had famously discovered ephedrine, the phenylethylamine derivative from the Chinese herb Má huáng (Ephedra vulgaris).(19)

Nagai had been mentoring a brilliant 24-year old chemist from Nashio-Nishinomiya named Keizo Uenaka (1876-1960) whom Nagai immediately offered up to Takamine.(18) Not only was Uenaka willing to move 12,000 miles away to Manhattan but he began detailed laboratory manuals in classical Japanese chronicling his work with Takamine, a record still kept in the Kyougyou-ji Buddhist archive in Uenaka's native Nashio.(20)

The Manhattan 'Adrenal' Project

Ueneka arrived in Manhattan in February, 1900 and began work in the lab in July utilizing the experimental procedures which he had mastered during ephedrine isolation with Nagai. Without modern air conditioning, and keeping all the windows closed for fear of excessive oxidation, Uenaka labored that first summer in the semi-underground laboratory, urged on by Takamine who supplied kilograms worth of bovine adrenal tissues from Parke, Davis & Co (Figure 2, 3). In Uenaka's manuals, he described how he first rejected the harsh sodium hydroxide alkalinizing step of Takamine's, and instead opted to macerate half the adrenal samples in water at 75~85°C for 8 hours; the other half in incubated in 95% alcohol at 82°C for 6 hours. The "alkaline liquid was left overnight until crystal precipitates were observed the following morning. The crystals were filtered with a paper, washed with water, and dried to generate a slightly brownish crystalline powder" via vacuum evaporation.(20, 21)

On the morning of August 4th, 1900, Uenaka exposed the crystals to ferric chloride and they turned green, a positive 'Vulpian' reaction. On August 13th, he utilized ammonia to improve crystallization. Takamine wrote that the product was "astoundingly strong....A fraction of one drop of (the) aqueous solution blanches the normal conjunctiva (of a mouse) within one minute... Three intravenous injections of 1 c.c. of the 1:100,000 solution in an 8 kilogram dog raised the blood pressure corresponding to 30 millimeters of mercury." Uenaka worked on optimizing the process over the next few months and ensured the derived products were different than Professor Abel's. Uenaka even took the daring step of experimenting on himself. "A drop of 1:1,000 acid solution of the new crystals was placed in one of my eyes," Ueneka wrote on October 13th, 1900 "(and) a drop of the aqueous extract of the (non-concentrated gland products) in another eye. The new crystal showed a stronger discoloration (of the eye) than the aqueous extract. So, it was concluded that the optimal dilution of new crystals for practical use should be 1:1,000." Prompted by the potentially exciting findings, Thomas Bell Aldrich, a former assistant to John Abel, and now working at Park, Davis, used a method slightly different from that of Takamine and Uenaka's to isolate crystals from the adrenal gland. Aldrich's end product was very similar to that of Takamine, their empircal formulas being $C_9H_{13}NO_3$ and $C_{10}H_{15}NO_3$, respectively, with the difference later determined to be due to a small amount of contaminating catechols (norepinephrine) in Ueneka's process. However, Aldrich did give credit to Takamine for being the first to derive crystallized adrenal extracts (without crediting Uenaka) and Takamine quickly moved to patent the "Glandular Extractive Product" as its

Figure 4. Cherry Trees around the Tidal Basin, Washington D.C. Takamine was a great philanthropist and famously arranged the Japanese donation of thousands of cherry trees to the United States in 1912. (T. Yamashima)

sole discoverer on November 5th, 1900 even prior to publication of the findings in academic journals.(22) He describes the step-wise process of obtaining the adrenal gland products in the first person singular only; there is no mention of the name "Uenaka". On November 7th, 1900, Ueneka writes that a friend of Takamine's, a certain Dr. Wilson, suggested a new name for the adrenal crystals and the term 'Adrenalin' came into existence. For fear of affecting Takamine's patent application, originality, and reputation, Uenaka dared not disclose the presence of his own Memorandum detailing his critical efforts, and he continued work on optimization steps. Only after Uenaka's death in 1960, when his son Mioji discovered the worn diaries, and provided them for translation from classic to modern Japanese by Aiko Yamashita, was the world informed of the true adrenaline discovery story. (21, 23)

Controversy

Takamine recognized the industrial value of adrenaline as he had of Taka-diastase years earlier. He completed five patent aplications for his extract (all of which were approved by June, 1903) and, by 1920, a total of eight patents would be filed and awarded. The discovery secure, Takamine and Ueneka moved back to Parke, Davis & Co. headquarters in Detroit in December, 1900 to continue the purification processes, presumably also with the help of Thomas Aldrich. Although the US patent office recognized Takamine's claims, rivals, including H.K. Mulford, contended one could not 'patent' a naturally occurring substance. The preeminent federal judge B.L. Hand (1872-1961) ultimately ruled in favor of Takamine but may have established a precedent for subsequent discoveries in nature so patented.(24) Meanwhile, at Park, Davis headquarters, the crystallization process was ramped up and nearly 200 grams of adrenaline crystal could be obtained from 8-20 kilograms of tissue or nearly 30 times what Uenaka alone could produce back in New York. In 1903, Abel formally admitted in a German chemical journal that "*(we) owe to Takamine (the) important observation that the substance can be precipitated in crystalline form from concentrated gland extracts by the aid of ammonia and other alkalies*. (In German)" (25)

In 1927, five years after Takamine's death, however, Abel wrote "the medullar hormone is called by various names (including) adrenaline and epinephrine, the latter…coined by me thirty years ago at a time when I supposed that the form in which I succeeding in isolating it represented the base as it actually exists in the capsules." It was at this time that Abel recalled receiving Takamine as a visitor in the fall of 1900 and that Takamine "*examined with great interest the various compounds and salts of epinephrine that were placed before him. He inquired particularly whether I did not think it possible that my salts of epinephrine could be prepared by a simpler process than mine, more especially without the troublesome and in this case wasteful process of benzoylating extracts of an animal tissue. He remarked in this connection that he loved to plant a seed and see it grow in the technical field*."(14) By the time time of Takamine's purported 1900 visit to Abel's lab, however, Uenaka had already derived the product that would ultimately be known as adrenaline. Still, Abel felt that "Takamine should have been successful only after his visit to my laboratory." With Abel's influence in international academic chemistry, his claim of being the first to isolate and name albeit an impure form of epinephrine, and Takamine's trademarking of the word "Adrenalin", "Epinephrine" gradually replaced "adrenaline" in the scientific literature. (2, 26)

Legacies

Takamine's investment in so many patents for Adrenalin paid off as the drug became widely employed in the medical community. Takamine used the royalties to enlarge his pharmaceutical research and business, but also to promote Japanese-American friendship. He founded the Nippon Club in 1905 and the Japan Society in 1907 both of which are active today in midtown New York City, although an earlier building had been shuttered by the United States in December, 1941. In 1912, Takamine played a major role in quietly obtaining the Japanese gift of thousands of cherry trees to the United States, trees which famously transformed West Potomac Park and the Tidal Basin in Washington, D.C. (Figure 4)(2, 18) Takamine himself had long suffered from liver ailments having undergone surgery for an acute condition in Chicago in the 1890's. He eventually succumbed to the disease on July 22nd, 1922 surrounded by his wife and their two sons in Lenox Hill Hospital. A memorial was held at the Nippon Club for the chemist, "perhaps the best-known Japanese in (the) country," before a funeral at St Patrick's Cathedral as Takamine had earlier converted to Catholicism.(27) He was buried at the Takamine family plot in the Bronx's Woodlawn Cemetery although his family deferred the scientist's desire that his body be used for science.(Figure 5)

DISCUSSION

The combination of hypothesis-testing and empiricism lie at the heart of scientific advancement. This manuscript portrays the isolation of adrenaline not as an isolated scientific leap, but after dogged, time-consuming research by Jokichi Takamine and Kezio Uenaka using the most basic chemical processes of the early 20th century. Takamine was a brilliant and pragmatic visionary who saw the isolation of adrenaline for its physiologic significance as well as its financial potential. Such a great discovery for mankind did not come without its controversies.

Takamine, for one, was Uenaka's employer suggesting a very intimate, trusting relationship between the two men. Uenaka may not have been fully aware of Takamine's objective to obtain a patent and gave Takamine the detailed information of the crystallization procedures described in both Uenaka's 'Experimental Memorandum' and Takamine's 'Laboratory Diary'. Some have surmised that Uenaka wished to protect Takamine's patent application, originality, and reputation, and dared not disclose the existance of his own Memorandum before and even after Takamine's death in 1922. It was only after Ueneka's own passing, in 1960, when his son Mioji found and reproduced his father's' laboratory manuals that Uenaka's true contribution to science became known. (20)

Abel himself appeared somewhat skeptical of the speed Takamine rushed to patent his findings, a feeling he articulated more widely after Takamine's death in 1922. As a professor of pharmacology at Johns Hopkins University, and a prolific writer, Abel's mindset was to publish scientific papers, not focus on patents and royalties.(14) Abel implicated that Takamine stole his technique of using ammonia at the final process of precipitation, suggesting that Takamine's achievement was essentially a copy of his experimental procedure. Since Takamine and Uenaka had already isolated adrenaline crystals before Takamine visited Abel's laboratory, Abel's position on any conceptual theft seems less likely. Abel's own efforts to purify adrenaline were stymied by contaminating benzoyl derivatives, but so too were Uenaka's adrenaline crystals slightly contaminated with noradrenaline which explained differences in chemical formulas when Aldrich tried his hand at the purification step later. Only the more sophisticated techniques of the 1940s, used by Ulf Svante von Euler (1873-1964), was finally able to differentiate and purify noradrenaline from adrenaline. Von Euler who was the first to demonstrate that noradrenaline is the main neurotransmitter in the sympathetic nervous system, and for such work was awarded the Nobel Prize in 1970, some 70 years after Takamine and Uenaka's discovery.(28) Abel himself was nominated for the Nobel prize on at least 12 different occasions in the 1920s; Takamine never lived to see such an honor.

As written in a 1928 remembrance, "*Time will dim the memory of his face, but it will only multiply his service to mankind, for wherever the substances of his discovery are used to assist a surgeon or physician, there will Dr. Takamine be present* (John H. Finley).(17)

As for Uenaka, he appears to have continued his work at Parke, Davis until 1916 when he relocated back to Japan to work in Sankyo Pharmaceutical Company (now Daiichi Sankyo) which Takamine had founded in

Figure 5. Final resting place of Jokichi Takamine, Takamine plot, Bronx's Woodlawn Cemetary. (T.Yamashima)

1913. But the deprivations of the second world war was difficult for Uenaka and his family, at times relegated to forging for edibles in the woods.(29) Uenaka appears to have been resigned to relative obscurity, working in his native province and living into his eighties. He made no subsequent claims to the discovery of adrenaline, even after Takamine's death, and his famous laboratory manuals may have perished were it not for the archival efforts of his son.

CONCLUSIONS

Jokichi Takamine and Keizo Uenaka were the first to crystallize adrenal extracts, Takamine for enabling the effort and patenting the discovery, and Ueneka for optimizing the technical steps for the process at the dawn of modern organic chemistry.

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The Evolution of the Management of Male Stress Urinary Incontinence

Karen M Doersch[1], Michael Witthaus[2], Gareth Warren[1], Ronald Rabinowitz[1], Divya Ajay[1,*]

From the (1) Departmet of Urology, University of Rochester Medical Center, Rochester, New York and (2) Department of Urology, University of California, San Diego School of Medicine, San Diego, California

**Correspondence: Department of Urology University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642; email: divya_ajay@URMC.Rochester.edu*

Introduction: The struggle to treat male stress urinary incontinence (SUI) dates back centuries, with descriptions of male urinary incontinence (UI) in Egyptian manuscripts as early as 1500 BCE. In this review, we chronicle the history of male SUI interventions that have evolved into the modern options available today.

Sources and Methods: A comprehensive literature review was performed to elucidate relevant historical and clinical information. We used PubMed to identify contemporary medical literature at www.ncbi.nlm.nih.gov and JSTOR, the digital library, to access archived, older texts at www.jstor.org.

Results: French surgeon Ambroise Paré is credited with developing the first portable urinals in 1564, which were quickly followed by Hildanus developing the condom catheter and penile clamp in the 1600s. The first documented compression device was developed by Lorenz Heister in 1747. Two hundred years later, Frederic Foley created a urinary sphincter and in 1973, F. Brantley Scott created the first multi-component artificial urinary sphincter (AUS). In the 1960s and 1970s, mesh implants were fraught with complications, including urethral erosion, fistulas, and pain. More recently, the transobturator male sling, which came to market during the 2000s, has become an option for select men.

Conclusions: The modern devices we use for the treatment of male UI are evolutionary byproducts of centuries of experimental designs by pioneering surgeons from around the world. While the materials have improved, barrier, storage devices and bulking agents almost identical to the versions first invented remain in use today.

Keywords: History, Male Urinary Incontinence, Reconstructive Urology, Urinary Incontinence Surgery

Male urinary incontinence (UI) has plagued humanity for generations. Currently, male UI affects up to 32% of elderly men and has a variety of etiologies. The first known mention of male UI is found in an Egyptian manuscript, the Edwin Smith Papyrus, from 1500 BCE.(1) Since that time, attitudes toward incontinence and strategies to address it have changed substantially. The goal of our paper is to outline the progress we have made in the management of male urinary incontinence.

SOURCES AND METHODS

A comprehensive literature review was performed to elucidate relevant historical and clinical information. We used PubMed to identify contemporary medical literature at www.ncbi.nlm.nih.gov and JSTOR, the digital library, to access archived, older texts at www.jstor.org.

RESULTS

Ancient Descriptions of Urinary Incontinence

The first written account of male UI was found in the Edwin Smith Papyrus, a manuscript written around 1500 BCE.(1) In this Egyptian manuscript, there is a detailed account of patients with various spinal cord injuries. One of the injuries, a cervical dislocation, resulted in motor and sensory loss of the upper and lower extremities as well as priapism and male UI. While the UI is not described in detail, it is impressive to note the specificity with which the author(s) describe the spinal cord injury level and their association of this individual's injuries, but not the several other spinal cord injuries described in the manuscript, with incontinence. However, this manuscript offers no therapeutic strategies for dealing with the incontinence it describes. Centuries later, Roman physicians described procedures for the management of urinary incontinence, such as the management of urinary fistulas.(2)

Modern Descriptions of Urinary Incontinence

Manuscripts from the 1920s mention male UI resulting from prostate surgeries, lack of bladder contraction, retention, tuberculosis affecting the urinary tract, or continuation of infantile incontinence. By the 1940s, physiologic descriptions of incontinence causes began appearing in the literature. Noted etiologies included iatrogenic causes, hypospadias, and bladder cancer.(3) Additionally, following World War II, incontinence secondary to spinal cord damage and other war-related injuries were described.(4) In the 1960s, it became more widely recognized that urinary incontinence could be the result of psychiatric disease.(5) In the 1970s, urodynamics was developed and aided in further characterizing incontinence in both males and females. Urodynamic studies both helped diagnose incontinent male patients but also led to further understanding of the roles of the various pelvic floor muscles in incontinence. In the 1980s, Edward McGuire refined urodynamics and investigated the technique for evaluating UI.(6) Today, urinary incontinence is categorized as SUI, urge UI (UUI), mixed UI, or overflow UI and treatment strategies differ depending upon the subtype of the UI.

Attitudes Towards Urinary Incontinence

Attitudes towards incontinence have evolved over the centuries. In the 1860s, Trousseau wrote about incontinence as though it were a remediable weakness in character, recommending punishment of incontinent children and shame for the elderly incontinent individuals.(7) Fortunately, by the 1920s, medical practice acknowledged causes other than flaws in motivation or personality, including iatrogenic causes such as prostate surgery, infectious causes such as tuberculosis, and physiologic weakness of the bladder. However, authors of this period continue to mention "persistence of infantile incontinence," indicating some limitations in understanding of the complexity of continence.(8) In the 1940s, authors began focusing more on physiologic causes of male UI and designing more specific mechanisms for managing incontinence based on etiology. Following World War II, patients with incontinence secondary to war-related injuries, such as spinal cord injuries, became an area of interest. Authors of this time period acknowledged both the physical and also the psychological impact of male UI.(4) Writers in the 1950s began to recommend respecting rather than blaming the incontinent patient. Nursing textbooks from this time period began to focus more on compassion and medical management, describing skin and catheter care, as well as recommending devices to make these patients more comfortable and easier to manage, such as the penile clamp or condom catheter. The 1950s

Figure 1. Early external urinary incontinence devices. (Left) Latex external bag urinary capture device. Right (Pediatric graduating penile clamp (Courtesy, Didusch Museum of Urologic History, Linthicum, Maryland)

is also the first decade in which incontinence began to appear in broader medical journals rather than just urological and gynecological journals. During the 1960s, several papers discussed incontinence secondary to psychiatric illness.(5) These papers typically focused on behavioral management strategies. The 1970s were a period of increasing understanding of the physiology of incontinence with the introduction of urodynamics as a diagnostic test for further characterizing incontinence.

Conservative Strategies

In the 1940s, there was an increasing interest in the rehabilitation of incontinent patients.(4) This was likely due to the increase in young and otherwise healthy individuals suffering from incontinence secondary to injuries sustained in combat during World War II. In 1951, Arnold H Kegel described pelvic floor muscle exercises as a therapy for incontinence.(9) Also in 1951, Alice Morrissey, a nurse now well-known for her focus on the role of nursing in the rehabilitation of various ailments, proposed a strategy for bowel and urinary bladder rehabilitation.(10) The employment of pelvic muscle exercises for UI management was further refined in the 1960s.(11) Some of these techniques are still practiced as part of pelvic floor rehabilitation today.

Storage and Drainage Devices

The renowned French surgeon Ambroise Paré is credited with developing the first portable urinals in 1564 (Figure 1). He developed a variety of portable urinals, which could be used by incontinent men, such as the "artificial yards," which were phallus-shaped and made from wood. In the 1600s, Wilhelm Hildanus, also known as the 'father of German surgery', created the first documented condom catheter made from pig bladder and strapped to the hips. Paré also developed catheters for insertion into the urethra. Paré was also the first to describe the coudé, or curved-tip catheter, for easier insertion.(12) Early urethral catheters, such as those developed by Paré, were rigid and used for intermittent catheterization only. Auguste Nelaton (1807-1873) designed the first rubber flexible catheter in the mid-19th century but the rubber dried too easily.(13) Frederic Foley, an American urologist, developed the first more flexible catheter out of latex in the 1940s. These and other more flexible catheters were not commonly used until a few decades later.(14) Flexible catheters were not only used for straight-catheterization but could also remain in place for longer-term drainage especially after the development of the 'bag' or 'balloon' catheter by Foley in 1929 and Hobert D Belknap in 1933.(13)

Barrier Devices

Barrier devices, including penile clamps and condom catheters, are now commonly used for male SUI (Figures 1 and 2). Penile clamps for external coaptation of the urethra were first invented by Hildanus. Subsequently, clamps were described in the 1740s-50s in a surgical textbook titled *Institutiones Chirurgiae*, authored by the German physician Lorenz Heister, which resulted in wider use of such devices. The Cunningham Clamp, introduced in 1910 by JH Cunningham, was based on these initial clamps, and became more popular throughout the 20th century (Figure 2). An alternative penile clamp, the Baumrucker clamp, was developed in 1979 and is also available on the market today.(15) Heister's text also described an external compression device for the bulbar urethra, by perineal compression. Another device for external urethral compression, the Vincent apparatus, was introduced by Vincent in 1960. This inflatable device is worn externally as a belt and compresses the perineum to coapt the urethra.(16)

Figure 2. (Left) The condom catheter, later incorporated in the April, 1967 patent by R. D. Davis (#3520305) to a collectible device and known thereafter as a 'Texas' catheter. (Right) Simple Cunningham Clamp (Courtesy, Didusch Museum of Urologic History, Linthicum, Maryland)

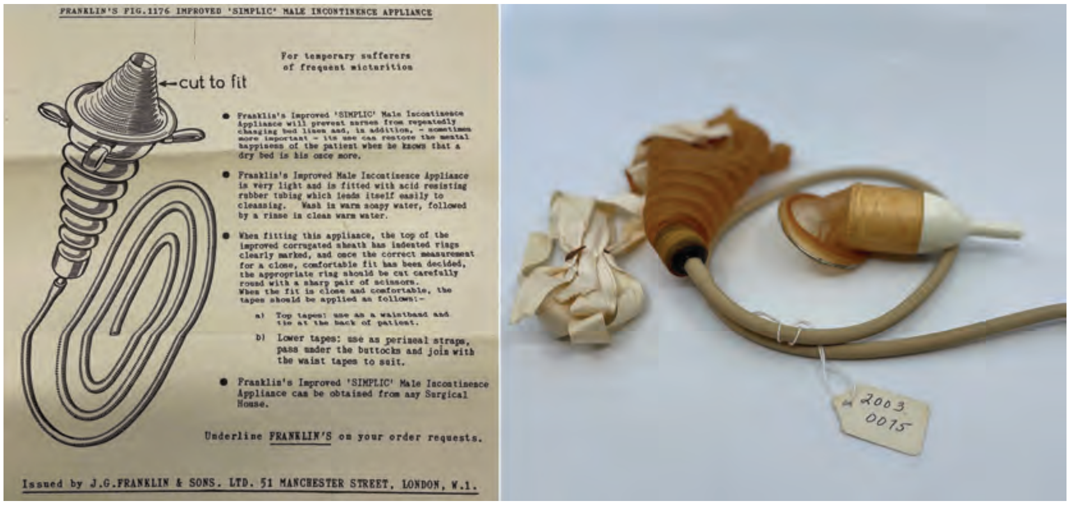

Figure 3. A British external device available after 1960 worn as 'Texas' catheter but with the ability to custom fit the ringed latex molding with helpful directions (Left) and a preserved sample (Right) (Courtesy, Didusch Museum)

Medical therapies

Oral medications to reduce male SUI began to appear in the 17th century. Over the centuries, a variety of oral therapies were tried, including opium, strychnine, and atropine, some of which produced anticholinergic and antidiuretics effects. Various topical treatments have also been tried to remedy incontinence as well. For example, in 1858, J. Rhodes described instilling a mixture of carbonic acid and chloroform into the bladder of an elderly male, resulting in improvement of nocturnal incontinence.(17) More recently, several studies have demonstrated the efficacy of duloxetine in managing post-prostatectomy SUI in men.(18) Duloxetine was associated with a dry rate of 25-89% and reduced mean pad number 12-100% after 1-9 months in various studies.(18) Adverse events associated with duloxetine therapy in this population included gastrointestinal symptoms, fatigue, dry mouth, insomnia, and reduced libido, and 21% of study participants discontinued duloxetine due to these side effects.(18)

Bulking agents

In the late 19th century, the Austrian surgeon Robert Gersuny began experimenting with injected paraffin for a variety of applications. One application he described was the use of paraffin as a urethral bulking agent. While the results were not particularly successful, this concept has continued to be explored. Subsequently, in the 1970s-1990s, other urethral bulking agents have been described, including Teflon, collagen, microsphere hydrogels, chitosan hydrogels, alginate hydrogels, and silicone.(19, 20) A randomized controlled trial comparing macroplastique to bulbar artificial urinary sphincter, found a success rate of the bulking agent to

Figure 4. Towards modernity. (Left) Inflatable cuff device for external penile use and (Right) a Rosen inflatable device, both circa early 1970s (Didusch museum)

be 47% at a mean follow up of 48 months (range 6 to 84 months).(21) A three-site injection technique was used and repeat injections were offered to patients who did not achieve continence after the first one. Retrospective studies on other agents report dry rates between 5.3 and 83%.(22)

More recently, the injection of stem cells has been described. Instead of serving as bulking agents to promote urethral coaptation, the injected cells are thought to decrease fibrosis and replace damaged cells, thus representing a step forward in injectable therapies.(23)

Surgical Approaches

One early surgical approach, described in the 1960s by Urologist Frank Hinman, involved the removal of the 7th rib and its subsequent attachment to the ischia of the pelvis to raise the urogenital diaphragm into a position that reduces the leakage of urine.(24) Also in the 1960s, John L Berry first described the implantation of acrylic mesh for the treatment of male UI.(25) The mesh was placed ventral to the bulbar urethra and fixed to the pubic ramus. Joseph J Kaufman, who worked closely with Berry, further refined this procedure, introducing hydrogel materials and different surgical approaches.(26) Kaufman's procedures included the Kaufman I, repositioning the crus of the penis to promote continence, the Kaufman II, which used a polytetrafluorethylene mesh, and the Kaufman III, which used an implanted silicone gel.(26) More recent sling implantations include the bone-anchored, adjustable retropubic, and trans-obturator approaches. Figure 4 demonstrates an early urethral sling. In 1947, the first artificial urinary sphincter (AUS) was described by Foley.(27) This pneumatic device was worn around an externalized, isolated portion of the corpus spongiosum. In the early 1970s, F. Brantley Scott demonstrated the first modern multi-component implantable AUS (Figure 5).(28) These devices had high success rates of continence and patient satisfaction. Further refinement of the AUS, with the addition of antibiotic coatings and redesigned cuffs, have improved outcomes for male UI sufferers. Other AUSs have also been described. The ZSI 375 made by Zephyr Surgical Implants is available outside the United States and has been shown to have low failure and complication rates.(29) Rosen et al created a silicone artificial sphincter, in which a three-pronged clamp compresses the urethra upon the inflation of an attached balloon.(30) However, trials of this sphincter have not been as successful as the sphincter initially created by Scott. The electronic version of the AUS is in development and greatly anticipated.

CONCLUSIONS

Male SUI is a long-standing problem that has been addressed by evolving strategies over time. Future studies of novel medical therapies or combination drug therapies will likely yield promising strategies for those seeking a medical solution to their incontinence. Implantable materials for the sling and AUS will likely continue to evolve, with the addition of more effective antibiotic coatings and materials that are less likely to erode. A bluetooth-based electronic AUS would represent a significant improvement, especially for those without the dexterity to operate a traditional AUS. Thus, as physicians and scientists continue to develop therapies, male UI management will continue to improve.

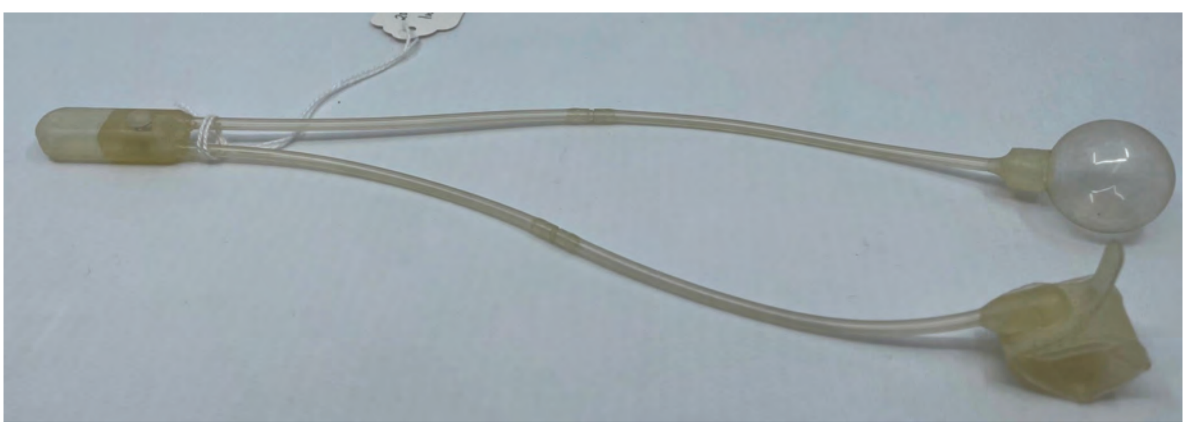

Figure 5. The first fully functional multi-component implantable artificial urinary sphincter by F. Brantley Scott (1930-1991) which, at the time of his death, had been placed in 25,000 patients (New York Times, 9/1/91 D, p 20) (Courtesy, Didusch Museum)

Figure 6. 'Incontinence controller', 1973, which was a transrectal means of providing electrical stimulation to the bladder (Didusch museum)

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Bullet Babies: The Repeating Nature of the Medical Hoax

Harry Herr*

From the Department of Urology, Weill Cornell Medical College New York, New York.

**Correspondence: Sectin of Urology, Memorial SLoane Kettering Cancer Center, 1275 York Avenue, New York, New York; e-mail: hherr@mskcc.org*

Introduction: Incredible tales of medical hoaxes associated with virgin births have been recounted through history. Some reports exist of wartime gunshot testicular injuries that caused pregnancy in a second bullet victim. This paper sought to identify the sources and circumstances of such tales and how similar legends appear to be perpetuated in medical historical lore.

Sources: Medical journals, contemporary newspaper accounts, and archives of secondary lay-press magazines and periodicals.

Results: The first known episode of a pregnancy conceived via bullet wound occurred in the American Civil War. A woman claimed to become pregnant from being shot by a bullet that had passed through the scrotum of a Civil War soldier. In reality, the tale had been fabricated by a doctor who wanted to tease his colleagues over their boastful surgical triumphs. A second such 'bullet baby' was reported in 1999 during the Bosnian conflict. The two episodes, despite their lack of medical credulity, were perpetuated in the medical press by reputable authorities.

Conclusions: History sometimes offers a storyline that may be so fantastical that even medical authorities may either disregard its impossibility or unknowingly prolong its life.

Keywords: Minie ball, virgin birth

Medical hoaxes and virgin births as isolated events are believed by some when authorities declare them plausible.(1) Some tales of cause and effect are so implausible, they strain the credulity of even the most gullible.(2,3) An example is the story of a woman who became pregnant from being struck by a bullet that had passed through the testicle of a Civil War soldier.(4, 5) Often ridiculed as a 'bullet baby' or 'son of a gun', a bullet-mediated pregnancy in a woman reportedly happened not once, but twice.(6) One of the cases has been repeated and retold in reputable medical journals, mostly lampooned as a hoax, but insisted by some as authenticated fact.(4,7,8). This manuscript sought to investigate the details of these reports, the individuals involved with them, and how these tales could be substantiated by medical authorities.

SOURCES

The manuscript surveyed archives of medical journals, the lay press periodicals, and contemporary newspapers from 1874 to the present that were related to the events of interest.

RESULTS

The Case of the Miraculous Bullet. On May 12, 1863, A Confederate Army doctor named LeGrand G. Capers was working in a field hospital in Mississippi, while the Battle of Raymond raged around him.(Figure 1) Three hundred yards behind the rebel lines was a house. On the porch was a mother and her two daughters, watching the action, ready to aid their fallen brethren. As the battle drew near to Dr. Capers, a soldier stumbled forward and fell to the ground. He had been shot in the leg, fracturing his tibia. The bullet "ricocheted off the bone and passed through his scrotum, carrying away his left testicle."(7) At the same time, Dr. Capers heard a piercing scream from the house. He addressed the soldier's wounds, when the mother from the house ran up and urged him to see her daughter. He complied and therein found a badly wounded young lady. A 'Minié' ball had "penetrated the left abdominal parietes, midway between the umbilicus and anterior spinal process of the ilium, and was lost in the abdominal cavity…". Believing the wound was mortal, and threatened by the enemy, Dr. Capers only had time to prescribe an anodyne before he was forced to retreat with his regiment.

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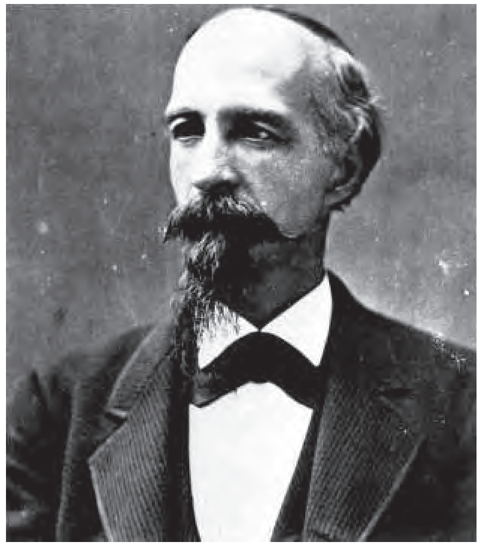

FIGURE 1 LeGrand G. Capers (1834-1877) hoped to be the anonymous author of the Pregancy-via-Minié Ball case were it not for the exceptional detective work of his editor who exposed the 1874 'caper'. Still, Dr. Capers had a long and, by all accounts, illustrious career in surgery and medicine, teaching at the New Orleans School of Medicine. His death, "stricken down in the glorious noon of his manhood", rocked Vicksburg (24).

He stayed behind in Raymond to care for the wounded and regularly visited the young girl. She suffered from peritonitis but remarkably recovered in two months. Six months later, Dr. Capers happened to be back in Raymond. He visited the girl and found she was in advanced stage of pregnancy. She insisted she was "pure and innocent" and had never had sex. Dr. Capers examined her and found the hymen intact. A month later, he delivered a healthy eight-pound baby boy, 278 days after the mother had been shot. Three weeks after the birth, the girl's grandmother asked Dr. Capers to see the child because there was "something wrong about the genitals." He detected a hard body embedded in the infant's scrotum and removed it. It was a Minié ball.

Dr. Capers agonized over this case and after several sleepless nights, he had an epiphany. He knew what must have happened. The Minié ball he removed from the infant was the same one that had wounded the soldier. "The bullet had plunged through the testicle," he conjectured "carrying particles of semen and spermatozoa into the abdomen of the young lady, through her left ovary, and into her uterus, and in this manner impregnated her. There can be no other solution of the phenomenon."(7) He informed the daughter who requested to meet the soldier. She married him and the couple had two more children the conventional way.

In 1874, eleven years later, Dr. Capers published his witnessed account in American Medical Weekly, a Louisville, Kentucky periodical.(7) He submitted it anonymously to disassociate himself from the article and as a joke to poke fun at the numerous, highly embellished, often spurious, Civil War stories then being told in the 1870s. The wily editor, Dr. E.S. Gaillard, was not hoodwinked. He recognized Dr. Capers' handwriting and printed the piece naming him as the author. The editor noted Dr. Capers disclaimed responsibility for the truth of that remarkable case of impregnation by a Minié ball....but "he does not say it is untrue, only that 'accidents may happen in the best regulated families.' " The editor punned "the readers have enjoyed the story much, but not enough 'to cut capers' after reading it."(9) Dr. Capers' intention was more serious in nature and clearly stated in the introduction of his account. "How common it is now-a-days," he wrote, "for men to tell wonderful stories about 'the war', their desperate charges, hair-breadth escapes, numbers who have fallen victims to their feats of personal valor, etc., etc. Then every surgeon has performed any number of wonderful operations before unheard of in the annals of surgery!"(7)

The Story Lives. After it appeared, this Civil War story became something of a legend. Its origins and details became obscured, but the basic outline of the tale was

FIGURE 2. The World Wide Web of Tales. (Left) Emmimarie Jones and her daughter, Monica, who was purportedly born via parthenogenesis, in post war Germany (Mirrorpix, London). (Right) This 1955 newspaper article by Audrey Whiting (Sunday Pictorial, London) on the Jones' case has been posted for years on the internet to depict the unrelated Bosnian 'Bullet Baby' case described in this manuscript although the latter purportedly occurred nearly 40 years later,(6,19)

frequently repeated. Dr. Capers' case of a virgin birth was portrayed usually as a humorous hoax but often as fact. As early as 1875, The Lancet reported the event as a veracious chronicle and it was further embellished in Anomalies and Curiosities of Medicine, published in 1896. (10,11) Even up to 1959, a respected obstetrician specialist in New York authenticated the tale as factual, asserting the incident could have happened, writing "no other solution to this birth was apparent."(4) In 1981, James Breeden sought to debunk the myth and tell the truth, declaring it a hoax (12). Dr. Capers was said to have "carefully recorded" the remarkable case "for the annals of medicine." "Doubtless", Breeden concluded, "many will pronounce the acts to be presently related as unusual or impossible; to such I need only to say, if not, why not?" Breeden asserts Dr. Capers was indeed poking fun at the braggadocio of his wartime colleagues. But the story did not end there. Dr. Capers' tale was reproduced in part again in The Lancet in 1989, by The Atlantic magazine in 2015, The Old Farmer's Almanac in 2018, and American History in 2019. (13-16) Even the television program "Mythbusters" devoted a whole episode attempting to see if a bullet-mediated pregnancy was possible.(17) They found that although a bullet could travel through a body and then another 300 yards, it could not penetrate a womb, nor could sperm survive the heat or friction of a rifled bullet.

Bosnian Bullets and Babies. An American woman in Bosnia gave birth to a baby girl, conceived, according to doctors, by a bullet that "pierced her stomach" after it hit a man in the testicles.(6) She claimed to be a virgin and thus represented the second reported case of a bullet-mediated pregnancy reported in the world.(Figure 2) Leslie Corbide was a nurse with the United Nations deployed in Bosnia in February, 1988 when she was wounded in a shootout between military police and a group of ne'er-do-wells. A bullet hit her in the lower abdomen. Six weeks later, complaining of absent menses and morning sickness, she insisted on a pregnancy test. A gynecologist who examined her discovered she was a virgin and was astounded when the test came back positive. In November, 1988, she gave birth to a baby girl weighing five pounds. The doctors were perplexed. Review of medical records showed that one of the police officers close to Carbide at the time was also shot. The doctors assumed the bullet hit the man's testicles, taking a small quantity of sperm to reach the uterus and inseminated Leslie. An analysis of the child and the father's genes demonstrated that the physicians' assumption was correct. No medical reports verifying the so-called 'virgin birth' are recorded. The story was rated "the most stupid piece of news of 2003."(19)

DISCUSSION

This manuscript investigated the details of two pregnancies in history potentially conceived through the high velocity traumatic transportation of spermatozoa from a father into the womb of the mother via bullet.

We found that there are two such tales of 'bullet babies' and that their permanence in folklore was perpetuated, in part, by their repetition and acceptance in bona fide medical professional and lay literature.(1,8,14) Dr. Caper's 'caper' has maintained its popularity for over 150 years despite a thorough dressing-down by the television program, "Mythbusters", which demonstrated that the inhospitable heat and trauma of bullet's projectory would preclude sperm viability.

There have been other instances where medical 'authorities' have validated and thereby perpetuated such hoaxes, a tendency of the self-serving that may even continue today. Nathaniel St. André (1680-1776), once personal physician to King George I, was duped by a one Mary Toth (1701-1763), who claimed to have given birth to a series of rabbits first reported by her obstetrician Mr. John Howard.(20) Mary's eventual confession cost St. André his career and livelihood, who himself refused to eat rabbits for the last 50 years of his life. (2) Complicity by medical doctors in these tales can even sway jurisprudence. In 1637, four physicians from Grenoble provided sworn avidavits that a young Magdeleine d'Auvermont could have become legitimately pregnant by her long-absent husband merely by dreaming of him. (21) Intentional hoaxes by medical men like Capers are also not unusual. Sir John Hill pseudonomously published articles on 'animalculi' which could float in the air and impregnate the ignorant, as an alternative to a contemporary 'spermist theory'of 'homunculi'.(22) Hoaxes, in this regard, seem to be a vehicle by physicians, like Drs. Hill and Capers, to exact revenge on the medical establishment through satire.(1)

Hoaxers, frauds, quacks, and charlatans are as old as the medical profession itself. Dr. Capers may have written his 'surgical triumph' in response to outlandish claims that had been given legitimacy in the medical literature which had no means of checking sources. His death in 1877 prompted the regular physicians of Vicksburg and Warren county to meet and discuss the legacy of their "friend and confrere."(23) "Stricken down in the glorious noon of his manhood...(he) was ever the same high-toned, honorable gentleman, rigidly adhering to the letter and spirit of the 'Code of Medical Ethics'."(24) Thus, it appears that his only known publication, while a satirical story, was viewed by his admiring colleagues as just that, a 'story'.

CONCLUSION

Impregnation by bullet may be physically impossible but, like other medical hoaxes, achieved some credibility when reported and authenticated by physicians.

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Professor Iglesias – Physician, Inventor, and Political Prisoner

Janmejay Hingu[1], Matthew Davis[1], , Hossein Sadeghi-Nejad[2], Mubashir Shabil Billah[3,*]

From (1) Rutgers New Jersey Medical School, Newark, New Jersey; (2) Veterans Affairs New Jersey Health Care System, East Orange, New Jersey; and (3) New Jersey Urology, Maywood, New Jersey

*Correspondence: *Mubashir Shabil Billah, New Jersey Urology, 255 Spring Valley Ave, Suite 101, Maywood, NJ 07607.*

e-mail: sbillah@njurology.com

Introduction: The Iglesias resectoscope is used around the world as an important tool in the urologist's surgical armamentarium. The biography of Iglesias himself, and how the resectoscope came to be, is less well known. We aimed to elucidate the background of the Iglesias instrument, its inventor, and his role in the development of modern transurethral resection techniques

Sources and Methods: We conducted interviews with surviving colleagues and students of Jose Iglesias, referenced secondary texts, and contemporary medical publications.

Results: Jose Iglesias was already a well-regarded urologist born in Havana Cuba having invented the instrument that bears his name in the 1950s. He was briefly imprisoned by the Castro regime after the Batista government was overthrown in 1959. His release through private funds brought him safely to the United States where he continued a long academic career at University of Medicine and Dentistry of New Jersey (UMDNJ).

Conclusions: Jose Iglesias was a Cuban urologist who invented the resectoscope that bears his name, After his paid release from a Castro-regime jail, Iglesias had a successful career at UMDNJ teaching decades of grateful residents

Keywords: Iglesias, resectoscope, biography, historical

Financial Support: none

For nearly a century, the transurethral resection of the prostate (TURP) has been the gold standard in the surgical management of benign prostatic hyperplasia (BPH). While the treatment of an enlarged prostate has advanced toward other modalities such as photovaporization of the prostate, water vapor therapy, and prostatic implants to open an obstructed prostate, TURP remains a tried-and-true option for many patients with BPH.(1) Over the past few decades, numerous modern advances have attempted to reduce drawbacks such as the risk of complications, performing the procedure in the operating room, and the associated costs of BPH surgical management. Despite all of these technological advances, TURP has remained the gold standard for reducing BPH symptoms, in no small part due to Dr. José J. Iglesias, the inventor of the continuous irrigation 'Iglesias' resectoscope. There is no published biography of the inventor in English, his background, or how his resectoscope was developed. We aimed to elucidate Dr. Iglesias' history to better understand the innovative significance of his contributions to urology.

SOURCES AND METHODS

We conducted interviews with alumni of the University of Medicine and Dentistry of New Jersey (UMDNJ) urology residency training program who worked under Dr. Iglesias in the 1970s. We referenced secondary and contemporary medical publications through the UMDNJ alumni association, the MEDLINE database of the National Library of Medicine (www.ncbi.nlm.nih.gov), the archives of the American Urological Association (AUA), Linthicum, Md., and US Immigration archives via ancestry.com

RESULTS AND DISCUSSION

Innovation. José J. Iglesias de la Torre was born in 1904 Havana, Cuba in a military household. (2) He graduated from and trained at the preeminent University of Havana School of Medicine in 1928 and became interested in the research and therapy of tumors of the bladder and prostate. Practicing at Cuba's Hospital

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Nuestra Señora de las Mercedes, he initially worked with the Stern-McCarthy resectoscope which utilized a rack-and-pinion mechanism for transurethral procedures. The working element was mechanically retractable which meant that the surgeon required two hands to operate; one hand held the scope while the other operated the cutting loop.(1) In contrast, Iglesias developed a resectoscope in 1945 that only required one hand, leaving the surgeon's other hand to fine-tune the flow rate, adjust camera settings, and stabilize the scope during the procedure.(2-4) Dr. Iglesias accomplished this by adding a counter force steel spring against the resecting mechanism. This provided tactile sensation and increased stability, allowing the surgeon to more accurately maneuver the resectoscope within their operating field. In his seminal 1948 report in the Journal of Urology, figures demonstrate how the instrument is held, and two surgical specimens, one of 150 grams and another of 250 grams, resected transurethrally at one sitting (4) Iglesias enlisted the help of American Cystoscope Manufacturing Inc. (ACMI) to manufacture and market his product, leading to the widespread adoption of the scope we see today. The instrument greatly improved clinical outcomes and Iglesias' surgical skills became legendary. As one of his prior residents Dr. Joseph V. DiTrolio put it, "when he would do a TURP, he would not be done until you could see capsule all around and (made) sure you could drink the water he was irrigating with."(5) As a result, many members of the Batista government and their allies chose Iglesias as their physician. Even internationally, he was well renowned. As Dr. Patrick N. Ciccone remembers it, "The King of Spain at the time personally flew Iglesias with all of his equipment out to do his TUR there."(6)

Imprisonment. Iglesias was a physician well-regarded by the Batista government in Cuba so when the Castro government rose to power in the 1960s, many members and allies of the previous Batista government were taken hostage, including Iglesias. Like many others, all of his belongings were immediately confiscated and he was thrown in jail, with Castro himself living in Dr. Iglesias' summer home at times.(6)

Soon after his capture, negotiations for Iglesias' release from prison began on his behalf. It became clear that the release would not occur without significant compensation to the Castro regime. The question then became how much would have to be paid to ensure his release. As recounted by numerous residents trained by Dr. Iglesias, his initial words were: "I'm not paying anything. I'm not going anywhere. I like it here in prison. Leave me alone." (5) As time passed, ACMI became involved in the negotiation. As ACMI was a small, family-owned business at the time, this made the plight of even a single associate a pressing issue for the entire company. ACMI had collected all of the royalties on the Iglesias resectoscope and stored them in an account in the United States. Much to the outrage of Iglesias, the company negotiated to turn over all of the cash royalties in order to let Iglesias go.(5) The money from

Figure 1. (Left) José J. Iglesias (1904-1979) pondering the instrument that bears his name. (Right) Dr. Iglesias (far right) pictured with Dr. Joseph J. Seebode (then Chief of Urology) and Dr. Madhav Kamat. (Courtesy Rutgers New Jersey Medical School Alumni Association (RNJMSAA))

the royalties was used to pay off Castro personally in order to get Iglesias out of prison. Considering the money paid was a large amount in the 1960s, losing it left Iglesias almost penniless afterward. He would often recount years later that, "It wasn't that bad in prison. I would have never given those bastards the money."(5)

An American Icon. Resilient as ever, Iglesias moved to New Jersey where he started right where he left off with his career in urology. During the 1970s, he became a professor at the University of Medicine and Dentistry of New Jersey (UMDNJ), now known as Rutgers-New Jersey Medical School. It has been hypothesized that this move for Iglesias, who was Catholic, may have been motivated by UMDNJ's prior Catholic affiliation back when it was known as Seton Hall Medical School. The exact reasoning, however, remains unclear. Over the next few years, he would train numerous UMDNJ residents.

In 1972, he and Manuel Ray, the Cuban engineer, gave as a gift to the AUA a prototype of the Iglesias resectoscope at the annual meeting in Washington, D.C. It was there he met representatives from the Karl Storz company which helped in further production of the instrument.(2) In that year, Iglesias was also elected to honorary membership in the New York Section of the AUA and donated one of his resectoscopes as a door prize for the 1974 Ferdinand C. Valentine resident essay contest.(7) At UMDNJ, he quickly established himself with the largely underprivileged patient population of Newark. Even years after leaving Cuba, many of the patients he used to treat back in Cuba would come back to have their surgeries done by him because of his reputation.(6) At UMDNJ and the East Orange Veterans Affairs hospital, Iglesias took on an active role in training residents and demonstrated his expertise. "Boss was a superstar," as Dr. DiTrolio recounts, "Iglesias ran a tight ship during his years there. He was very strict on how he wanted things done and his approach was meticulous, as if he was given the instructions for surgery straight from Mount Olympus."(5) Given the rigor of training, graduates recount leaving the program extremely well-prepared and educated for their own practices.

While working at the University Hospital, a mechanism for continuous irrigation, which was perhaps Iglesias' greatest contribution to improving the resectoscope and related endoscopic procedures, would come to fruition. By engineering a continuous irrigation mechanism into the resectoscope, his invention allowed the surgeon to resect tissue without intermittently stopping to empty the bladder. As Dr. Ciccone recounts, "He and I were the first ones to try this continuous flow concept."(6) Continuous flow led to lower intravesical pressures and irrigant usage,

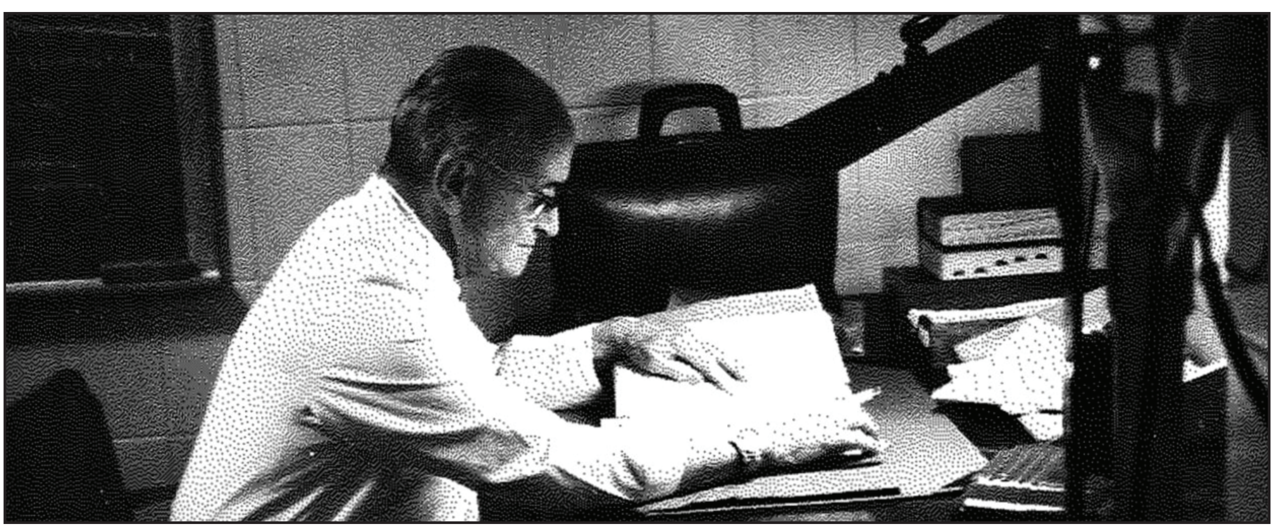


Figure 2. Dr. Iglesias pictured in his study (courtesy RNJMSAA)

Figure 3. Grand Rounds, Department of Urology, with Dr. Iglesias in attendance (2nd from left, 2nd row) (Courtesy RNJMSAA)

thereby reducing the risk of TUR syndrome.(8) Thanks to Iglesias' ingenuity, this mechanism is now found in all modern-day resectoscopes. Jose Iglesias lived to see his invention used and incorporated in urologic clinics, operating rooms, and teaching programs through the world, reaching the age of 75 at the time of his passing in Elizabeth, New Jersey.

CONCLUSIONS

Overall, Dr. Iglesias made multiple contributions to the field of urology with the invention of the Iglesias resectoscope and its utilization of continuous flow irrigation.(9) Even after decades of continued technological advances in the surgical management of BPH, TURP remains the gold standard, in no small part due to the fact that the Iglesias resectoscope revolutionized transurethral prostate treatment. Despite his wrongful political imprisonment and its inherent adverse effects on limiting further contributions to the field, Iglesias' work has made a lasting impact that will continue to benefit future generations of urologists and their patients.

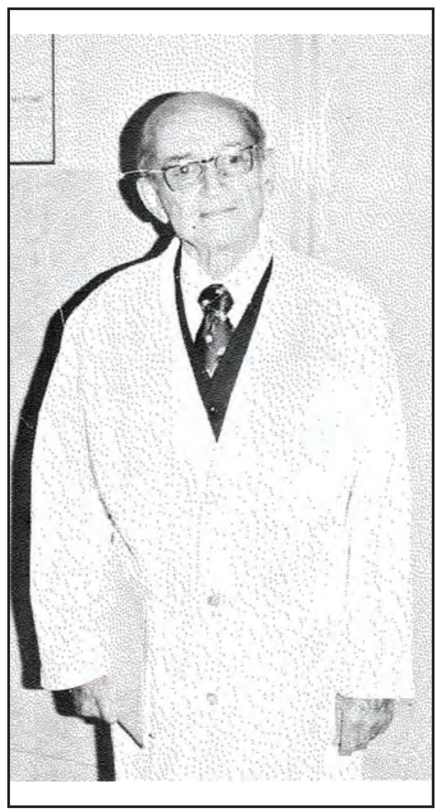
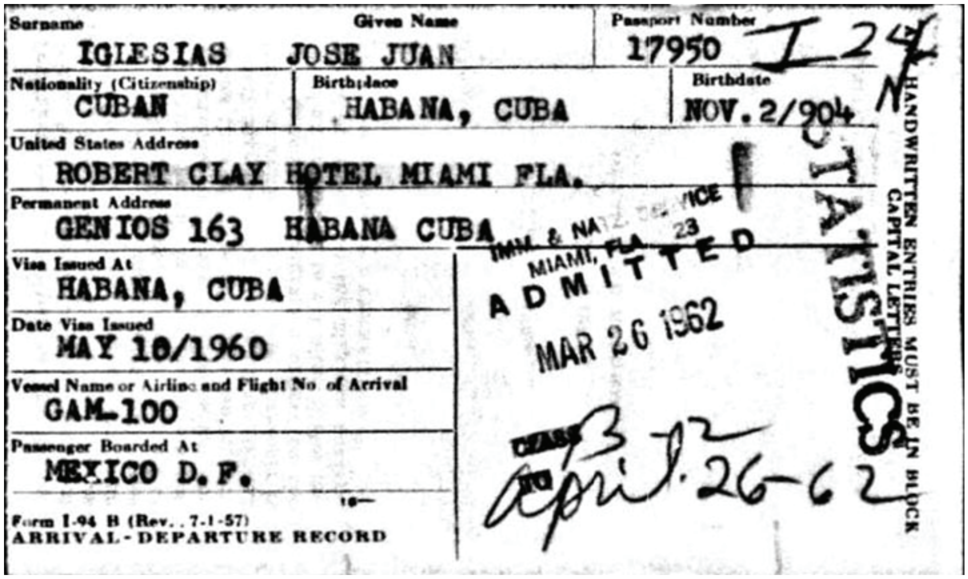


Figure 4. Jose J. Iglesias de La Torre (1904-1979) (Courtesy, RNJMSAA)



Surname IGLESIAS
Given Name JOSE JUAN
Passport Number 17950
Nationality (Citizenship) CUBAN
Birthplace HABANA, CUBA
Birthdate NOV. 2/904
United States Address ROBERT CLAY HOTEL MIAMI FLA.
Permanent Address GENIOS 163 HABANA CUBA
Visa Issued At HABANA, CUBA
Date Visa Issued MAY 10/1960
Vessel Name or Airline and Flight No. of Arrival GAM-100
Passenger Boarded At MEXICO D. F.
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ARRIVAL-DEPARTURE RECORD
ADMITTED
MIAMI, FLA.
MAR 26 1962
April 26-62
HANDWRITTEN ENTRIES MUST BE IN BLOCK CAPITAL LETTERS

Figure 5. Admissions document, spring, 1962, for Dr. Jose Iglesias, upon his permanent arrival to the United States, from Cuba, via Mexico, and after his long political imprisonment by the Castro regime (National Archives, Washington, D.C.)

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BIO-SNIPPET: THE 'OTHER' PROUST- ROBERT PROUST (1871-1922)

Figure 1. (Inset) Robert Proust, 1922. (Main) Illustration of Proust by A. Chanteau, 1907, and captioned "Here is Proust holding the prostate he has just removed from the patient under the white blanket." (Both courtesy, BIU Santé – Université de Paris)(1)

Marcel Proust (1871-1922) wrote his ground-breaking works *Remembrances of Things Past* in the early 1920s when Europe was still reeling from the trauma and catastrophe of the Great War. Proust's work, which is lauded as one of the greatest in the canon of western literature, famously made manifest on paper, through self-analytical stream-of-conscious thinking, and sometimes paragraph-long sentences, the universal feelings of love, loss, mystery, and emotion that typifies the process of growing up. At the age of 51, Marcel died a near recluse, probably of tuberculosis, but cared for by his brother, Robert, a Parisian uro-gynecologist who, at the time of Proust's unbridled creativity, was certainly the more famous sibling. Robert (1873-1935), had trained under the pioneers of modern French urology, Felix Guyon (1831-1920) and Joaquín Albarrán (1860-1912), and had, by the 1900s, become an international expert in his own right of perineal, simple prostatectomy. Proust was lauded by his peers, some of whom referred to a prostatectomy and a 'proust-atectomy'.(2) Chanticlair, a French periodical from 1906-1936, which celebrated writing, poetry, and art, also highlighted contemporary medical or scientific personalities of note through biography and portait. Proust himself was featured in caricature for a 1907 issue of Chanticlair, a common form of reverence of the time. (Figure 1)

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BIO-SNIPPET: THE 'OTHER' PROUST- ROBERT PROUST (1871-1922)

Figure 1. (Inset) Robert Proust, 1922. (Main) Illustration of Proust by A. Chanteau, 1907, and captioned "Here is Proust holding the prostate he has just removed from the patient under the white blanket." (Both courtesy, BIU Santé – Université de Paris)(1)

Marcel Proust (1871-1922) wrote his ground-breaking works *Remembrances of Things Past* in the early 1920s when Europe was still reeling from the trauma and catastrophe of the Great War. Proust's work, which is lauded as one of the greatest in the canon of western literature, famously made manifest on paper, through self-analytical stream-of-conscious thinking, and sometimes paragraph-long sentences, the universal feelings of love, loss, mystery, and emotion that typifies the process of growing up. At the age of 51, Marcel died a near recluse, probably of tuberculosis, but cared for by his brother, Robert, a Parisian uro-gynecologist who, at the time of Proust's unbridled creativity, was certainly the more famous sibling. Robert (1873-1935), had trained under the pioneers of modern French urology, Felix Guyon (1831-1920) and Joaquín Albarrán (1860-1912), and had, by the 1900s, become an international expert in his own right of perineal, simple prostatectomy. Proust was lauded by his peers, some of whom referred to a prostatectomy and a 'proust-atectomy'.(2) Chanticlair, a French periodical from 1906-1936, which celebrated writing, poetry, and art, also highlighted contemporary medical or scientific personalities of note through biography and portait. Proust himself was featured in caricature for a 1907 issue of Chanticlair, a common form of reverence of the time. (Figure 1)

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