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SPECIAL ARTICLE

The contribution of women to pancreatic knowledge☆

Aportación de la mujer al conocimiento pancreático

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Introduction

Long ago, the profession of doctor was forbidden to women. The first female doctor was Agnodike in Athens in the fourth century BC, but she had to disguise herself as a man to study and practice.[1] In the tenth century, a medical school was set up in Salerno which was not controlled by the Church and women were allowed access; they were called the ''Ladies of Salerno''. Among them was Trótula de Rugiero, who wrote several treatises on paediatrics and gynaecology which were used up to the 16th century, although from the 12th century some copyists attributed them to her husband, Johanes Platerius, and the name of the author evolved to Trottus.[2]

In the nineteenth century, women were still banned from studying Medicine. Margaret Ann Bulkley (1795–1865) had to disguise herself as a man and call herself James Barry in order to study Medicine and join the British Navy as a doctor. It was not until her death that a post-mortem examination revealed her true gender. She carried out the first caesarean section in which both the mother and the child survived.[3]

Following the suffragist movements in the nineteenth century, universities gradually began to open up to women and allow them access to learning in different disciplines. One of the pioneers in the field of Medicine was Elisabeth Blackwell (1821–1910), a British emigrant to the United States who, after a tour of ten medical schools, was finally accepted at the Geneva Medical College in New York, and in 1849 became the first woman in history to qualify as a doctor.[4] Her sister Emily (1826–1910) also graduated in medicine in 1854. Cecilia Grierson (1859–1934), born in Buenos Aires of Scottish descent, was the first woman to practice as a doctor in South America, dedicating herself to gynaecology and obstetrics.[5] Also important was Florence Nightingale (1820–1910), an Englishwoman born in Italy, founder of modern nursing and of the British Red Cross on her return from the Crimean War (1853–1856), where she had worked as head of a group of nurses who saved the lives of thousands of soldiers by improving hygiene and sanitary conditions.[6]

In Spain, the pioneer was Dolors Aleu i Riera (1857–1913), from a bourgeois Catalan family, who in 1874 began studying at the Faculty of Medicine in Barcelona, finishing brilliantly in 1879. Nevertheless, she was not able to take her degree exams until 1882 because of bureaucratic obstacles for the fact that she was a woman. She specialised in gynaecology and paediatrics.[7]

Once they had overcome the difficulty of being able to study, the next issue was lack of recognition of the work of women in the field of medicine. There are countless awards for recognising the excellence of particular types of work carried out by a few outstanding people. Among the most important are the Nobel prizes, which have been awarded since 1901.[8] By 2017, a total of 26 organisations and 902 people had been given awards, 212 corresponding to the

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Nobel Prize in Physiology or Medicine. Of those, only 11 were awarded to women.[9]

Reviewing the literature, we were unable to find any publications referring to a compilation of women whose research helped to expand knowledge and understanding of the physiology and diseases of the pancreas. Our aim with this article is therefore to pay tribute to the women who, with their wisdom and tenacity, have contributed to expanding our understanding of the pancreas.

The protagonists

Julia Dempsey (Sister Mary Joseph) (1856–1939) (Fig. 1)

Julia Dempsey was the first to draw attention to the presence of a periumbilical subcutaneous nodule (Fig. 1) which corresponded to a metastasis of an intra-abdominal neoplasm, one of the most important of which is pancreatic cancer. In 1949, the British surgeon Hamilton Bailey used the eponym ''Sister Mary Joseph nodule'' for the first time in the eleventh edition of his manual 'Demonstrations of Physical Signs in Clinical Surgery'.[10] It is the only eponym that bears the name of a nurse. Years before, in 1928, William Mayo, surgeon with whom the sister worked, had described this sign before the Cincinnati Society of Surgery, but unfortunately without mentioning Sister Mary Joseph. He called it ''*pants button umbilicus*'' (trouser button navel).

Julia Dempsey was the daughter of Irish immigrants, and at 22 years of age, along with two of her sisters, she joined the congregation of Saint Francis, choosing the name of sister Mary Joseph when she was ordained. Because of her organisational skills, the order moved her in 1889 to Rochester, to the recently opened Saint Mary's Hospital, founded by the surgeon William Worrall Mayo (1815–1911) with the help of the congregation. The hospital would later become known as the Mayo Clinic. The first directors were the surgeon's sons, William James and Charles Horace. Sister Mary Joseph did not have any nursing knowledge when she arrived at the hospital, but she quickly acquired it with the help of the nurse and future wife of Charles Mayo, Edith Graham, and was soon appointed head nurse. The following year she became assistant to William James Mayo. The Mayo brothers specialised in abdominal surgery, both urgent and deferred, and William published the first case of resection of a pancreatic islet cell carcinoma.[11] Sister Mary Joseph was responsible for making the first incision and closing the surgical wound once the procedure was completed. In 1906 at the initiative of Sister Mary Joseph, the hospital created a School of Nursing that would later obtain official accreditation.

She died of pneumonia on 29 March 1939 and was buried in the Saint Joseph cemetery in Rochester.[12,13]

Figure 1 Sister Mary Joseph (Julia Dempsey). Named the periumbilical subcutaneous nodule, which was given her eponym and indicates metastasis of an intra-abdominal tumour, one of the most important of which is pancreatic cancer. It is the only eponym that bears the name of a nurse.

Virginia Kneeland Frantz (New York, 1896–1967)

In 1959, Virginia Kneeland Frantz described a very rare pancreatic tumour (1–2% of all pancreatic neoplasms) characterised by the fact that it mainly affects young women. It also has an indolent clinical course and can therefore reach a considerable size. It has a low malignant potential so has a good prognosis. The tumour can be distinguished by having liquid and solid areas with pseudopapillary formations in its interior. It was initially known by the eponym Frantz's tumour.[14] However, it subsequently received several other names, including Hamoudi's tumour,[15] papillary cystic neoplasm and solid papillary cystic neoplasm, and is now known as solid pseudopapillary tumour of the pancreas.

Virginia Kneeland Frantz graduated in chemistry in 1918 and later enrolled at the Columbia University College of Physicians and Surgeons in New York, where she was one of five women among the 74 students who were accepted. She graduated in 1922 and two years later became the first female surgeon at Columbia University, associated with the Presbyterian Hospital. In 1927, Frantz left the clinical side to work in the Pathology laboratory of the same hospital, where she studied pancreatic, breast and thyroid tumours. In 1935, she described the secretion of insulin in neuroendocrine pancreatic tumours along with her colleague, the prestigious surgeon, Allen O. Whipple. She was pioneer in using radioactive iodine to locate and treat metastatic thyroid cancer. In 1959, she wrote a chapter on pancreatic tumours for the 'Armed Forces Atlas of Tumour Pathology', in which she described the tumour that bears her name. Between 1924 and 1962, Frantz taught surgery at the Columbia University College of Physicians and Surgeons. She was president of the New York Pathological Association (1949–1951) and elected the first female president of the American Thyroid Association (1961–1962). In 1967, the year of her death, the School awarded her with the institution's Silver Bicentennial Medal in recognition of her contribution to the teaching of medicine.[16]

Dorothy Hansine Andersen (North Carolina 1901–New York, 1963)

In 1938, Dorothy Hansine Andersen described the symptoms and histological changes of the pancreas of children with a new disease she called ''cystic fibrosis of the pancreas''.[17,18] The term cystic fibrosis had been used by the paediatrician Guido Falconi von Grebel (1892–1979) in 1936 to describe the association of exocrine pancreatic insufficiency and

chronic lung disease in children. Despite the importance of his publication, Falconi did not make the impact he might have expected. In 1946, Andersen conducted a series of studies on family members of patients with cystic fibrosis that allowed her to conclude that it was a genetic disease transmitted by autosomal recessive inheritance.[19] That same year she and the paediatrician Paul di Sant'Agnese (1914–2005) used penicillin in aerosol and sulphonamides to treat lung infections in these patients, but they did not obtain the results they had hoped for.[20]

Dorothy Andersen was of Danish descent. She was awarded a degree in Medicine at Johns Hopkins University in 1926. Her goal was to be a surgeon, but she was denied access to the residency programme for this specialist area because she was a woman. Consequently, in 1929 she joined the Department of Pathology at Columbia University's College of Physicians and Surgeons. The following year she became an instructor in Pathology at the university. In 1935, she started working as an assistant pathologist at Babies Hospital at the Columbia-Presbyterian Medical Centre. It was here, when performing a post-mortem examination on a child with suspected coeliac disease, that her attention was drawn to the hardened pancreas. This led her to investigate and she concluded that it was a new disease, which she called ''cystic fibrosis of the pancreas''. Andersen also investigated diseases caused by glycogen storage and congenital heart diseases, which led her to collaborate on cardiac surgery training programmes. In 1958, she was named head of the Pathology Department at Columbia-Presbyterian Medical Centre and professor of Pathology at the University of Columbia. She was a heavy smoker and died of lung cancer in New York on 3 March 1963.

Dorothy Crowfoot Hodgkin (Cairo, 1910–Shipston-on-Stour, United Kingdom, 1994)

Nobel Prize for Chemistry in 1964 for ''her determinations by X-ray techniques of structures of important biochemical substances''.[21] She determined the three-dimensional structure of insulin and other substances such as penicillin and vitamin B12. The sequencing of the amino acids in insulin (the first sequenced protein) had been known since 1955 from the work of Frederick Sanger, but it was Dorothy Crowfoot who published the rhomboidal structure of insulin at a resolution of 2.8 Å.[9] She deciphered its complex three-dimensional structure made up of 777 atoms, studies she had started in 1934.

Dorothy Crowfoot Hodgkin was born in Cairo to English parents dedicated to archaeology. Later they moved to Sudan and then to Palestine. Living with two archaeologists, she decided to devote herself to the chemistry applied to archaeology. In 1928, she went to study at Somerville College at the University of Oxford, where she remained until 1932. She studied crystallography, and under the direction of her tutor F.M. Bewer, investigated the application of X-rays to this science. This technique is used to determine the three-dimensional structures of biomolecules. She studied for a time at Cambridge, where she conducted research into sterols. In 1934, she returned to Oxford and taught chemistry in women's colleges. Among her students in 1940 was one who would later become prime minister, Margaret Thatcher.

Figure 2 Stamp published in 1996 in homage to Dorothy Crowfoot Hodgkin which has a photo of her and part of the three-dimensional structure of insulin that she described.

That same year, with the help of Sir Robert Robison (a professor at the University of Oxford who would be awarded the Nobel Prize in Chemistry in 1947 for his studies on alkaloids), she began to seek funding, which she eventually received from the Rockefeller and Nuffield Foundation, which allowed her to continue the studies she had started in Cambridge on sterols and begin in the field of other substances, such as insulin (1934), penicillin (1942)[22] and vitamin B12 (1948).[23]

She worked intensively in the investigation of the structures of many different biochemical substances until, in 1964, she became the third woman to receive the Nobel Prize in Chemistry. Marie Curie had received the Nobel Prize in Chemistry in 1911 (for the discovery of polonium) and also the Nobel Prize in Physics in 1903 for the discovery of radium. Her daughter Irène Joliot-Curie was awarded it in 1935 for the synthesis of radioactive elements. Crowfoot Hodgkin was awarded several honorary titles, among which are the Honorary Foreign Member of the American Academy of Arts and Sciences (1958), Order of Merit (1965), Copley Medal of the Royal Society of London, Lenin Peace Prize, Chancellor of the University of Bristol and an Austrian award for Science and Art (1983). She was one of five women selected for a collection of British stamps published in August 1996 (Fig. 2).

Crowfoot suffered from rheumatoid arthritis for many years and died on 29 July 1994 following a domestic accident.

Rosalyn Sussman Yalow (New York, 1921–2011)

She received the Nobel Prize in Physiology or Medicine in 1977 for ''the development of radioimmunoassay of peptide hormones''.[24] She used this technique to measure hormones, including circulating insulin. She shared the prize with the Frenchman Roger Guillemin (born 1924) and the Pole Andrew Viktor Schally (born 1926), who, separately, discovered somatostatin, the sites where it is synthesised (brain, stomach, intestine and pancreas) and its mechanisms of action.[8]

Yalow came from humble origins. At an early age she showed an interest in reading, maths and physics. She was

fascinated by reading a biography of Marie Curie published by her daughter Eve (concert pianist, journalist and writer) and a lecture given in 1939 by the Italian physicist Enrico Fermi (Nobel Prize in Physics, 1938) at Columbia University, which awakened her interest in physics. She studied at Hunter College for girls in New York and later, in 1941, she moved to the University of Illinois, being the only woman among 400 students, the first since 1917. In 1945, she returned to New York and started working in the Federal Telecommunications Laboratory. She was the only female engineer in the company. She received her doctorate in nuclear physics in 1947 and joined the radiotherapy department of the Bronx Veterans Hospital, where she worked her entire working life, dedicating herself in a very special way to the study of radioisotopes. In 1949, Yalow opened her own laboratory and a year later met Salomon Aaron Berson, with whom she worked closely for 22 years, until his death in 1972. Soon both were interested in the technique of radioimmunoassay, which they applied to the study of insulin metabolism in patients with type 2 diabetes. They observed that over time these patients developed antibodies against the insulin administered, demonstrating that a small protein could cause an immune response. The article in which Yalow intended to publish her finding was initially rejected, until they simply removed the word ''antibody'' from the title, as suggested by the editor of 'The Journal of Clinical Investigation'.[25,26]

By studying the reaction of insulin with antibodies they realised that they had developed a tool with the potential to measure circulating insulin. As a result of the development of this method, it gradually became possible to determine the plasma concentration of different hormones and other substances circulating in the blood in minute quantities. One of these substances is serum trypsin, measurement of which in a sample of dried blood on absorbent paper helps identify whether or not a newborn may suffer from cystic fibrosis.[18]

Neither Yalow nor Berson ever wanted to patent their analytical method despite the potential financial impact. Thanks to their findings, the era of radioimmunoassay is considered to have begun in 1959, and their method has been used to measure hundreds of substances of biological interest in thousands of laboratories around the world.[11]

In addition to being awarded the Nobel Prize in Physiology or Medicine in 1977, Yalow was a member of the National Academy of Sciences, and in 1976 she received the Albert Lasker Basic Medical Research Award. She received honorary doctorates from the universities of Hartford and Connecticut.

She died in New York on 11 May 2011.

Hilda J. Tracy (Birkenhead, United Kingdom, 1927–2010)

In 1964, Hilda J. Tracy defined the chemical structure of gastrin and discovered that levels of this hormone were increased in patients with Zollinger-Ellison syndrome,[27,28] a condition described in 1955 by Robert Milton Zollinger and Edwin Homer Ellison.[29,30]

She studied at the University of Liverpool, where from 1950 she worked as a research assistant on the team of physiology professor Roderick Alfred Gregory (1913–1990). From 1958 until her retirement in 1993 she was a professor in that same Physiology Department. Between 1962 and 1968 Tracy worked with Gregory on the sequencing of gastrin, using hundreds of pig stomachs in the process. She also showed that the carbon terminal 4 of the amino acid residues was responsible for gastrin activity.[31]

Catherine Figarella (1935–2017)

Born in France, Catherine Figarella was a world expert in the isolation and characterisation of proteins from the human exocrine pancreas. She described numerous zymogens, such as human trypsinogen 1, proposing the hypothesis that premature intracellular activation of this zymogen could play a fundamental role in the pathogenesis of chronic pancreatitis. She also showed that a similar phenomenon occurs in cystic fibrosis.[32]

Once Figarella graduated, after a period of indecision, she decided to pursue research. In September 1960, after having defended her doctoral thesis on pancreatic enzymes in June, she began working in the laboratory of Professor Pierre Desnuelle at the Faculty of Sciences of Saint Charles in Marseille. Her field of research was the study of the pancreatic enzymes of different animal species. Also in Marseille, she worked in the Gastrointestinal Pathology Research Unit of Professor Henry Sarles, who was especially interested in chronic calcifying pancreatitis.[33]

Figarella's hypothesis of the premature intrapancreatic activation of trypsinogen 1 was clearly supported by the discovery made by David C. Whitcomb in 1996, demonstrating the existence of a genetic mutation of trypsinogen 1 in hereditary pancreatitis.[34,35] She collaborated with Jean-Pierre Chazalette and Jacqueline Carrère, of the Renée Sabran Hospital in Giens-Hyères, who had over 300 patients with cystic fibrosis under follow-up, and this enabled her to study the behaviour of serum immunoreactive trypsin in these patients.[36] Doctor Figarella died on 12 April 2017.

Julia Margaret Polak (Buenos Aires, 1939–London, 2014)

In 1973, Julia Margaret Polak, Stephen Robert Bloom and Anthony G.E. Pearse coined the term ''VIPoma'',[37] a name used for the pancreatic neuroendocrine tumour described in 1958 by the American internal medicine specialist John Victor Verner and the Irish-American pathologist Ashton Byrom Morrison. These tumours, also known as Verner-Morrison syndrome, are characterised by watery diarrhoea, hypokalaemia and achlorhydria. Other names include pancreatic cholera, WDHA syndrome (from watery diarrhoea, hypokalaemia, achlorhydria) and watery diarrhoea syndrome.[11] Polak and Bloom worked at London's Hammersmith Hospital under Pearse, and coined this name after identifying vasoactive intestinal peptide as the causative agent of the syndrome.

Polak came from a Jewish family which had fled from Eastern Europe at the beginning of the Nazi occupation. She graduated from the Faculty of Medicine in Buenos Aires in 1961 and specialised in pathology. In 1967, she moved to London, where her husband, the haematologist Daniel Catovsky, had secured a grant. She started post-graduate studies at

Hammersmith Hospital with Professor Antony G.E. Pearse (1916–2003), an expert in histochemistry who contributed to the discovery of the APUD (amine precursor uptake and decarboxylation) system, and she would continue to work with him after she completed her studies. In 1984, Polak was appointed Professor of Endocrine Pathology at Hammersmith Hospital's School of Medicine, and, in 1991, Head of the Histochemistry Department. Using histochemistry, she also demonstrated the existence of nitric oxide at the nerve endings.

In 1995, Dr Polak had to have a heart and lung transplant after having developed serious idiopathic pulmonary arterial hypertension. From that moment, she changed her field of interest from pathological anatomy to tissue engineering. She used stem cells to generate tissues. In 1998, with biomedical engineer Larry Hench, she created the Centre for Tissue Engineering and Regenerative Medicine at Imperial College London. In 2003, Queen Elizabeth II named her Dame of the British Empire. She died on 11 August 2014 at the age of 75.[38]

Joan M. Braganza

Joan M. Braganza was born in India in 1943 and studied Medicine at the Grant Medical College in Bombay, graduating in 1966. She has investigated different possible aetiologies of different forms of chronic pancreatitis.

She travelled to the United Kingdom and in January 1968 joined the reference unit for chronic pancreatitis at Manchester Royal Infirmary directed by Henry T. Howat, a European pioneer in pancreatology, who had introduced the use of pancreozymin in the classic secretin-stimulation test for the study of pancreatic exocrine function.[39] In 1974, Braganza was appointed as a senior lecturer in Medicine at the University of Manchester, and continued to work in Professor Henry Howat's unit. She occupied the position of consultant gastroenterologist at Manchester Royal Infirmary from 1978 until her retirement.[40] In 1982, she published a study showing that there was no direct association between the degree of morphological damage in the pancreas in chronic pancreatitis and the state of exocrine function.[41] She also demonstrated the utility of treatment with antioxidant micronutrients to improve progression and pain in recurrent chronic pancreatitis, in order to avoid or at least delay surgery.[42]

In 1998, Braganza confirmed the existence of mutations of the CFTR (cystic fibrosis transmembrane conductance regulator) gene in 15–45% of cases of idiopathic pancreatitis, particularly among the younger cases, while no cystic fibrosis manifestations were identified.[43,44]

She was president of the Pancreatic Society of Great Britain and Ireland in 1990 and retired early in 1998.

Lluïsa Guarner Aguilar (Barcelona, 1949–2012) (Fig. 3)

Lluïsa Guarner Aguilar was the first woman to become involved in pancreatic pathology in Spain, and published numerous studies on diseases affecting the pancreas.

Born into a family of gastroenterologists, she was the oldest of eight children. She graduated in Medicine at the University of Barcelona in 1972, doing her residency at Barcelona's Hospital Clínic. In 1976, she published her first work, related to the Lundh test for studying pancreatic exocrine function.[45] Two years later, Guarner Aguilar joined the Gastroenterology Department of what is now Vall d'Hebron Hospital in Barcelona, where her interest in pancreatology grew. In 1984, she defended her doctoral thesis entitled, ''Immunoreactive trypsin and serum lipase: utility in the diagnosis of pancreatic disease''. It was one of the first theses about the pancreas presented in Spain. That same year Guarner Aguilar was appointed Head of the Gastroenterology Section, carrying out both patient care and research work. In 1989, she was co-founder of the *Asociación Española para el Estudio del Páncreas* [Spanish Association for the Study of the Pancreas], now called *the Asociación Española de Pancreatología* [Spanish Association of Pancreatology]. In 2002, she was one of the three editors of the book *Tratado de páncreas exocrino* [Treatise of the Exocrine Pancreas]. Two books relating to this subject had previously been published in Spain: the first in 1923, in Madrid, by the Basque-born doctor Luis Urrutia (1876–1930), and the second in Barcelona in 1956, by Vicens Artigas (1908–1975), a surgeon at Barcelona's Hospital de la Santa Creu i Sant Pau.

Figure 3 Lluïsa Guarner Aguilar, the first woman to become interested in and work in pancreatic pathology in Spain.

Guarner Aguilar was the first woman to be elected president of the *Societat Catalana de Digestologia* [Catalan Society of Digestology], a role she performed from 2003 to 2006. She was also vicepresident of the *Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears* [Catalonia and Balearic Islands Academy of Medical and Health Sciences]. In 2007, she received the Josep Trueta Medal for Merit in Healthcare in recognition of her patient care and research work. In 2012, shortly before her death, she was one of the founding members of the *Societat Catalana de Pàncrees* [Catalan Pancreas Society]. In 2016, this Society began to award the annual *Premi Lluïsa Guarner* [Lluïsa Guarner Prize] for Research in Pancreatic Pathology to honour the best published work on the pancreas by members of the Society.[46]

Guarner Aguilar wrote many articles on acute pancreatitis[47] and chronic pancreatitis,[48] pancreatic cancer,[49,50] cystic fibrosis[51] and especially on genetic

mutations and the effect of coffee and smoking on these disorders.[49,52,53]

She died of lung cancer on 30 July 2012.

Final reflection

This article describes a representative series of women who have contributed to our increased understanding of the pancreas in spite of the difficulties they have had to face for the mere fact of being women. There are undoubtedly many more who equally contributed, but who have been forgotten. The feminisation of medicine is now a reality all over the world. At the Medical College of Barcelona, women make up 47% of the members. The proportion should increase before too long, as 74% of medical students in Spain are women.[54] Consequently, within a few years, many medical services and research centres will be headed by women. This should lead to women obtaining more resources for research and so female names should become increasingly more visible in scientific publications. We must therefore hope that in the short-to-medium term we will see an increase in the degree of recognition of their work.

Conflicts of interest

The author declares that he has no conflicts of interest.

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