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SHORT COMMUNICATION

Lady Andromache (Mary) Papanicolaou: The Soul of Gynecological Cytopathology

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This commentary serves to impress the astonishing and selfless contributions that Andromache (Mary) Papanicolaou made toward the scientific development of the Papanicolaou (Pap) test; for she alone was, and remains, the hidden soul of gynecological cytopathology. The odyssey assumes even greater significance as 2014 marks 100 years since the beginning of this saga at Cornell Medical College. An awareness of the background historical details and events is important and relevant to this commentary. Her kindness, thoughtfulness, and devotion to her husband, Dr. George N. Papanicolaou, and his work, shall survive her indefinitely through the Pap test and through the women surviving cervical cancer globally as a result of their combined revolutionary scientific work.

In 1890, Andromache Mavroyeni was born into the family of a prominent military officer of the Greek army. During her childhood years, the Mavroyeni family secured a beach house on the island of Euboea near the small coastal town of Kymi overlooking the Aegean Sea. There they resided during the hot summer months, just a short ferry ride from the city of Athens. It was during these holiday excursions that they became acquainted with the neighboring family of Dr. Nicholas A. Papanicolaou, a respected local physician.[1-3]

From an early age, Andromache wanted to be called "Mary." It was not long during her summer stays in Kymi before she developed a friendship with Helen, the youngest of the four Papanicolaou children, and younger sister to George Papanicolaou.[1]

Their friendship lasted a lifetime despite the years and distance that separated them. Andromache, it seems, was destined for greatness but not without sacrifice.

In retrospect, it is difficult to differentiate between what may have been destiny or mere coincidence. But from these humble beginnings and later from truly coincidental

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encounters, diagnostic medical science has witnessed an epic odyssey revolving around 2 people devoted to each other, and, equally so, to the painstaking experimental work they conducted that led to the development of the Papanicolaou, or Pap, test − the life-saving screening test for cervical cancer.

From a scientific standpoint, this commentary serves to impress the astonishing and selfless contributions that Andromache (Mary) Papanicolaou made for this odyssey; for she alone was, and remains, the hidden soul of gynecological cytopathology. The odyssey assumes even greater significance as 2014 marks 100 years since the beginning of this saga at Cornell Medical College.

Moreover, the salient human events instill a sense of emotional amazement, and a sense of boundless responsibility given the revolutionary science inherited by every diagnostic cytologist and patient surviving cervical cancer.[1-3]

Information pertaining to Andromache is scarce and scattered. Therefore, an awareness of the background historical events (as gathered from Greek and English literature) is important and relevant to this commentary to provide frames of reference.

In 1883, George was born in Kymi and, customary to Greek culture, was christened George Nicholas Papanicolaou (*George* being his maternal grandfather, and his middle name identifying his father). He grew up to be a bright but sentimental boy increasingly mesmerized by nature around him, but more particularly by the sea, by its mysteries and welling energy. His personality and principles seemed fashioned by the sea. His attempt to join the Greek Navy at the age of 13 ended in failure; he was declined because of his age. Nonetheless, one aspect of his personality, through to the end, was his ability to muster constructive energy and resolve from the polarizing forces that oftentimes accompany ardent desire and sudden disappointment.

George was intelligent and adept in academics. He was also warmly influenced by his mother, Maria. He nurtured a lifelong connection to her gentleness and passion for music, which he inherited through his ability to play the violin. Her motherly affection was manifested through the violin during critical times in his life.

Dr. Nicholas Papanicolaou wanted George to study medicine and assist him to develop the family practice in Kymi. George foresaw this as something standing between him and his desire to study natural phenomena, to research the unknown, and to somehow give back to life something that would be beneficial for humanity, and, worthy of him.

George entered the University of Athens in 1898 to study music and the humanities. Soon after, he switched into medicine, graduating with honors in 1904 at the age of 21.

Now a physician, Dr. George N. Papanicolaou was promptly enlisted into mandatory military service, which he completed on August 15, 1906. He had been thus promoted to medical reserve officer, but kept advising his father of his disfavor toward a medical practice in Kymi. Regardless, George returned to Kymi only to face uncertainty and growing dissatisfaction. On the island, he felt disorientated from mainstream knowledge and study. Despite his steadfastness, however, George's humanity emerged as he periodically attended to the medical needs of a leper colony north of Kymi, alongside magnificent yet treacherous coastal rock formations. There, George reconnected with the Aegean reviving his passion for scientific research.

During this period of indecision and soul searching, an unexpected encounter was to eventually alter his life.

In the late summer of 1906, young Andromache Mavroyeni, then 16, became ill and needed the attention of a physician. Responding to the suggestion from a concerned neighbor, Dr. George Papanicolaou agreed to visit the Mavroyeni family to offer his support. It was then that he first met Andromache, his sister's friend. After her recovery, Andromache became a regular visitor to the Papanicolaou homestead. But George remained detached, looking westward, yearning to study German and Darwinian philosophy and cellular biology.

Concerned, Dr. Nicholas Papanicolaou eventually agreed to support his son to attend graduate studies in Germany, initially at the University of Jena. It was during his doctorate work pertaining to sex differentiation in water fleas, and gamete fertilization in other organisms, that George devoted his life to biological science and research. He completed his doctorate in 1910 and immediately thereafter returned back to Greece with hopes of conducting scientific research there. He soon found that to be a far-fetched impossibility due to the lacking infrastructure.

While back with his family in Kymi, he faced the prospect of marriage to the daughter of a wealthy merchant, as proposed and negotiated by his father. However, he did not agree to this proposition. Instead, he decided to leave. These uncomfortable circumstances led him to yet another serendipitous encounter that finally crystalized his purpose and direction in life.

While on the ferry toward Athens, he found himself in the company of the Mavroyeni family heading home after their summer vacation. He found Andromache, now 20, to be highly attractive, cultured, and educated. She played a piano on board the vessel, and he accompanied her on the violin as they performed familiar scores. George became infatuated with Mary, and his desire for her grew during the various engagements he attended as a guest in the Mavroyeni homestead in Athens. With indecision now aside, he asked for Andromache's hand in marriage. After gaining consent from her father, Colonel Mavroyeni, the couple married in a small private ceremony on September 25, 1910. Fearing adamant disapproval by George's father, the Papanicolaou family back in Kymi was not notified of the wedding, and this decision weighed heavily and painfully on George for the remainder of his life. He agonized for failing his parents' love toward him and for his toward them.

While on their honeymoon, the couple decided to search for employment opportunities in Europe. To assist them,

Colonel Mavroyeni secured first-class passage on the ocean liner *Athenai* sailing for Marseilles. From their scouting efforts in Europe, Dr. Papanicolaou eventually gained employment in the Oceanographic Museum in Monaco as marine zoologist classifying marine life forms. He immediately wrote to his parents in Kymi to proudly announce his first stable income and his marriage to Andromache. Dr. Papanicolaou eventually accompanied Prince Albert I of Monaco on the oceanographic vessel *L'Hirondelle II*, surveying Mediterranean species.

Shortly thereafter Dr. Papanicolaou received word of his mother's passing. This was a lasting wound. And as he had completed his obligations at the museum, the couple departed for Kymi as requested by his father, who was in mourning.

Soon after returning to Greece, Dr. George Papanicolaou was recalled back into military service in the run up to the Balkan War, which started in late 1912. Following this conflict, he was determined to relocate to America. He misguided his father by declaring he had secured employment there, and despite passionate objections raised by both their families, he was poised to leave Greece indefinitely. Despite the uncertainties, Andromache did not resist. Her nature was largely passive; she was characteristically agreeable, wanting her husband to live his dreams. Her only preoccupation was he, and this never wavered. Colonel Mavroyeni reluctantly provided them trans-Atlantic passage again toward North America. The couple sailed on the *Athenai* — the same vessel that transported them to Marseilles for their honeymoon cruise 2 years earlier.

They landed in New York, as registered immigrants on October 19, 1913 (Fig. 1). With little more than merely dreams, themselves, and $250, they embarked on a new life of work and study in their new homeland. Neither spoke English fluently.[1]

Their new lives were fraught with difficulties. Language was but 1 major problem. Others were the need for stable employment and adequate income in an unfamiliar setting. Bewilderment soon enveloped them. George did not want to raise a family that would create any additional hardships or obstacles in his quest for scientific research. Andromache agreed.

She was the first to find employment sewing buttons on garments in Gimbels department store for $5 a week. But not being able to communicate in English and her long working hours were painful difficulties. Disheartened, she wept when home after work.

Dr. Papanicolaou had also accepted a rug salesman position in the same department store, but abandoned this post on his second day due to humility. He supplemented Andromache's income by playing the violin and writing freelance articles about general biology.

In Europe, World War I was declared in July 1914, dashing any prospect of return.

It was therefore fortunate that Papanicolaou met Dr. Thomas Morgan of Columbia University who had just published a book entitled *Heredity and Sex*, in which some of Papanicolaou's doctoral research was cited. Morgan was a distinguished zoologist in America studying *Drosophila*, and it was through him that Papanicolaou eventually met Dr. Charles Stockard, chairman of the Department of Anatomy, Cornell Medical College, New York. From this encounter, and based on favorable recommendations, Papanicolaou was offered the position of assistant anatomist and thus officially joined Cornell in September 1914.

Figure 1 George and Andromache Papanicolaou after arriving in New York in 1913. Reprinted, with permission, from Charles C Thomas Publisher.

In November 1914, Andromache also joined Cornell, volunteering as technical assistant to her husband.

At this juncture, 3 key elements of the Pap test odyssey had converged. Other elements were also destined to appear in due course. Yet, the collaboration between Drs. Stockard and Papanicolaou and Mrs. Andromache Papanicolaou embodied the nucleus igniting revolutionary work and discovery. This team produced seminal publications that ultimately founded the discipline of diagnostic cytopathology.

Stockard was studying the transmission of alcohol-induced chromosomal damage to guinea pig offspring. In 1915, he redirected Papanicolaou's attention toward X and Y chromosome analysis also in guinea pigs relative to sex determination. This work necessitated the study of animal ovum age and status, which also necessitated precise determination of ovulation;

however, all of this was essentially impossible with sacrifice of the animal, which then negated further study of sex development. The impasse was perplexing.[2,3]

Papanicolaou knew he had to time ovulation. He also knew that these small mammals menstruated. As neither of these phenomena was obvious to him, he pondered if vaginal fluid could somehow reveal ovulation.

It was this simple curiosity that changed the course of events and redefined the remainder of Papanicolaou's life, career, and legacy, and that of his wife's. Diagnostic gynecological cytopathology was thus conceived.

He obtained a small nasal speculum and through it proceeded to take miniscule vaginal fluid samples from the experimental animals daily to look for clues. The analytical and microscopy skills he acquired in Germany proved invaluable. From meticulous record keeping and analysis, Papanicolaou discovered characteristic epithelial cell patterns in the vaginal fluid smears of guinea pigs that ultimately revealed ovulation precisely. He also documented the epithelial phases that repeated throughout menstrual cycling and correlated them with uterine histology and therefore to ovarian physiology. A sea of discovery emerged from a sole curiosity. These findings were published with Stockard in 1917,[4,5] and although within the research domain, Papanicolaou introduced the rudimentary bases of diagnostic cytopathology along with fundamental terminology describing the altering morphology of epithelial cells as noted microscopically relative to their surroundings.

In the background, the technical work was performed by Andromache. She managed the smear samples, staining of cells, and record keeping following the microscopic analyses to support their publications.

In 1919, Papanicolaou received notice of his father's passing. This additional wound came at great cost to him, and he struggled to stay on course. He did not just lose a father, he also lost a driving force. Yet history has shown that these losses were supplanted by Andromache.

Papanicolaou was a trained physician, although neither hired nor licensed as such in New York. It was therefore natural for him to question whether the same physiological phenomena and epithelial cell alterations noted microscopically in small mammals may also occur in women.

Having no access to patients, he turned to Andromache.

She willingly produced the samples required to support his studies. Papanicolaou took regular vaginal fluid samples from his wife. Andromache's contribution of cellular study material lasted an astonishing 21 years. She was also involved in processing, staining, and organizing her own samples for ongoing analysis. And from this marathon study, she ultimately donated the foundations on which gynecological cytopathology was developed. During this timeframe, Papanicolaou was able to study cellular alterations throughout a woman's life from child-bearing age through to menopause. He was also able to correlate the associated endocrinology and bacterial flora. Additionally, he was able to perfect the Papanicolaou vaginal smear technique and the Pap staining method, which was strategically designed to reveal subtle nuclear and cytoplasmic alterations reflecting hormonal status, thus cell maturity and viability. All in all, it was through Andromache's samples that Papanicolaou described physiologically normal gynecological cytomorphology. This substantial baseline knowledge formed the backdrop against which cellular abnormality would later be differentiated and graded.[2,3]

Papanicolaou continued analyzing Andromache's samples until 1925 when he decided to include samples from other volunteering women, some being followed for cervical disease. Hence, it was inevitable that he would eventually discover abnormal epithelial cells in vaginal fluid samples exfoliating from cervical cancer.

The experimental technique now demonstrated immense clinical potential. Papanicolaou quickly sensed an opportunity. His overall work, as supported by his technical assistant Andromache, spawned numerous publications describing the cytomorphology of abnormal cervical epithelial cells.

Three years later, convinced that his technique and its diagnostic application were beyond doubt, he presented these revelations with excitement in the landmark report "New Cancer Diagnosis" at the First Race Betterment Conference in Battle Creek, Michigan, in January 1928.[6] But nothing could have prepared them for the startling disappointment. The presentation excited few and failed to spark enthusiasm. Papanicolaou was not a pathologist, and cervical disease was conventionally followed through surgical biopsy. In the few months that followed his presentation, Papanicolaou's discovery and thesis appeared in the local newspapers, but they were essentially overshadowed as the Great Depression ushered in a decade of hardship posing other priorities. There was little interest in medical diagnostic novelty. The vaginal smear method was considered superfluous by leading pathologists and gynecologists.[3]

This setback was deeply overwhelming. Disheartened, Papanicolaou ceased his study of abnormal cells and abandoned the concept of cervical cancer detection. Instead, he continued to study donated samples from Andromache analyzing hormonal effects on cervical epithelial cells. This phase lasted a decade but proved significant in the discipline of diagnostic cytopathology. From this study, Papanicolaou introduced the science of gynecological endocrinology and its effects on the cervical epithelium as detected through the vaginal fluid technique and the exfoliated cells using the Pap stain.

The tides were destined to reverse in 1939 with the death of Dr. Stockard as his successor, Dr. Joseph Hinsey, asked Papanicolaou to reconsider his concept of cervical cancer detection after reviewing his impressive publications. Hinsey was another key element of the Pap test odyssey. Hinsey also introduced Papanicolaou to Dr. Herbert Traut, another key element, as he realized Papanicolaou needed a collaborator knowledgeable in gynecological pathology.[1-3]

The teamwork between Papanicolaou and Traut produced fundamental work and one of the most notable of cytological publications in 1943 after their analysis of thousands of cases, the monograph *Diagnosis of Uterine Cancer by the Vaginal Smear*.[7] This publication redefined gynecological cytopathology with the remarkable illustrations of epithelial cells in water color, by the master scientific illustrator at Cornell, Hashime Murayama (Fig. 2). The collaborators confessed that fine cytomorphologic detail would have gone unnoticed had it not been for Hashime's talent and skill.

Andromache worked closely with Hashime to carefully organize the cases and recreate on paper the cellular features noted microscopically. She was in essence, the master manager (Fig. 3).

The monograph and its follow-up publications captured the attention of the medical community. And the application of the vaginal fluid technique for the detection of incipient cervical cancer took hold with expanding application. Eventually, another key element of the odyssey, Dr. Charles Cameron, who was the director of the American Cancer Society, sponsored the First National Cytology Conference in Boston, in 1948, to showcase the remarkable success of this method in detecting early cervical disease relative to

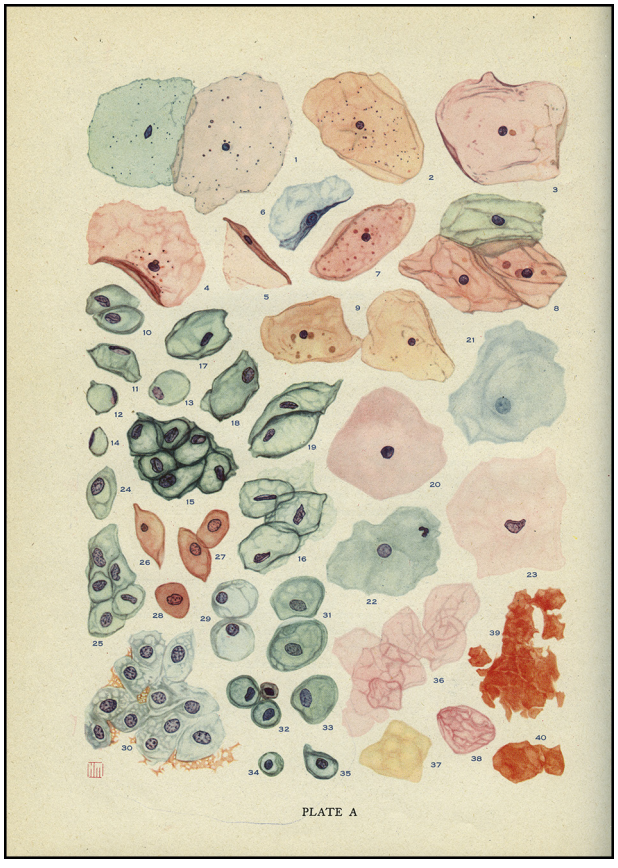

Figure 2 Epithelial cells found in the vaginal smear of women (normal sex cycle, pregnancy, postpartum). Reprinted, with permission, from The Commonwealth Fund.

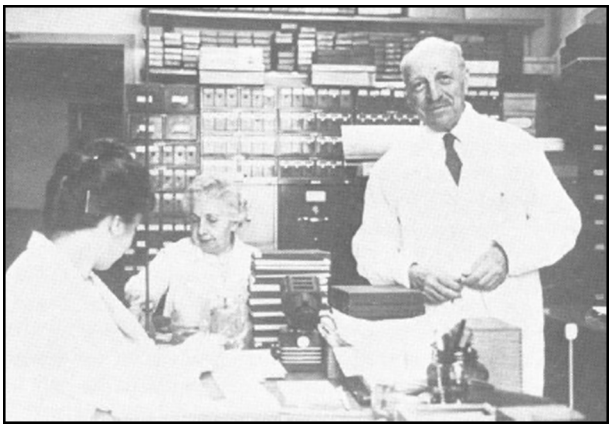

Figure 3 Mrs. and Dr. Papanicolaou, cytology laboratory, New York Hospital-Cornell Medical Center. Reprinted, with permission, from Charles C Thomas Publisher (undated photo).

cervical biopsy. Following years of trials, and increasing acceptance, Cameron formalized the vaginal smear method christening it as the "Pap test" in 1954.[1-3]

Along with Murayama, Dr. Papanicolaou produced yet another masterpiece publication in 1954, the *Atlas of Exfoliative Cytology*.[8] This historic book encapsulated his overall experience with the Pap test method and introduced nomenclature by which epithelial cell abnormality may be systematically graded and reported. This system became known as the Pap Classification Reporting System.[3,9]

For the next 3 years, Papanicolaou was heavily involved in teaching cytopathology, and he spoke at numerous conferences and conducted tutorials. Photographs from these tutorials reveal Andromache and Hashime sitting modestly among the audience, as they always had been in the background of this epic saga. Andromache took charge and taught cytotechnology in their laboratory, and the various methods they had developed. It has been said that she was the first technical cytologist and the first ever Pap test recipient. Her technical work survives them well into modern cytopathology practice through publication and demonstration. The Papanicolaous had received scores of pathologists, gynecologists, and cytologists from all over the world at Cornell Medical College to demonstrate cytological techniques and diagnoses. They showed cases from their vast collection. These efforts, as declared by Dr. Traut, were "largely responsible for the spread of the use of this method in various parts of the world."[10]

In 1957, after becoming Emeritus Professor of Anatomy at Cornell Medical College, Dr. George N. Papanicolaou retired. Both he and the volunteering Mrs. Andromache (Mary) Papanicolaou gave that institution 43 years of uninterrupted service. Finally, the couple decided to take their first formal holiday since 1913. They returned to Kymi for their first time since leaving Greece. This visit was painful as the parents they left behind were no longer there to greet them. They wished their parents could have known of all

their successes and been proud of them.[1-3] Papanicolaou had exchanged numerous letters with his family back in Greece in which he repeatedly acknowledged how blessed he felt given the partnership and marriage he enjoyed by Andromache's side.

Likewise, Andromache included her comments in their correspondences assuming a role of "mother mediator" throughout the various matters that arose over the years. Their nieces and nephews became their beloved children, and they participated actively in their upbringing in various ways.

Always looking forward, Papanicolaou considered opening a cytopathology research institute in either America or Greece, but he could not find fertile environments in order to do so. He therefore continued to practice cytopathology from his home and provided consultation services maintaining his usual, grueling work ethic.

Nevertheless, Andromache had her own way of sensing and softening setbacks. She convinced George to relocate into a larger home on Long Island with a splendid garden located near the seaside. There she wanted him to reconnect with the ocean and absorb its energy.

According to Carmichael,[1]

> Mrs. Papanicolaou continued to manage all household affairs… On the weekends, Mrs. Papanicolaou herself prepared delicious Greek specialties. Her love was the garden and Dr. Pap remarked that she had "two green thumbs." But Mrs. Pap's chief concern was the welfare of her husband and she made certain that he never wanted for anything which she could provide. Cold orange juice was kept in a thermos on his desk at the laboratory and on the table beside his bed. A sandwich and fruit were brought to the office so that Dr. Pap would not have to waste time eating in the cafeteria. Mrs. Pap usually had lunch with the laboratory technicians whom she helped train. She also drove back and forth to work while Dr. Pap read or listened to the news.
>
> On arriving home, generally after dark, the couple had dinner and then listened briefly to classical music, usually Beethoven or Bach, then Dr. Pap resumed his study until midnight or after.

In 1958, Papanicolaou was once again nominated for the Nobel Prize in Medicine. However, he found himself dismayed and deeply discouraged on receiving notice that he was declined for this prestigious, global award.[1,3,11,12]

Shortly thereafter, Papanicolaou began to dream incessantly, expressing marked interest in studying parapsychology. This sudden departure alarmed Andromache. She sensed a looming crisis. She insisted he stay focused on cytopathology as more good was there to come for him. And it did, as according to her intuition. Papanicolaou was distracted by a surprise invitation for him to direct the Cancer Institute of Miami. After much consideration, and passionate pleas advising them against the idea from their friends, the Papanicolaous predictably ignored the odds and accepted the offer, and relocated to Miami in 1961.

The institute was to be renamed in Dr. Papanicolaou's honor on his next birthday on May 13, 1962. The dedication indeed happened but without him as he had died due to heart failure on February 18, 1962, at nearly 79.

Mrs. Andromache Papanicolaou embodied the essence of gynecological cytopathology. She not only donated a wealth of study material, she also painstakingly applied scientific methods alongside her husband to develop an effective clinical screening test to spot incipient cervical disease. The Pap test has saved countless lives since its inception and formalization owing largely to her work and contributions. The world, specifically in regions where robust mass screening programs have been implemented since the mid-1950s, has witnessed a remarkable decline in the incidence and mortality rates associated with cervical cancer.

Andromache aged gracefully. She was invited to attend numerous events in which she was honored and applauded for her work and also received various awards on behalf of her husband (Fig. 4).[1]

She was awarded a Special Citation from the American Cancer Society in 1969 with the following inscription,[13]

> Special Citation to Mrs. George N. Papanicolaou who recognized greatness and served it and whose intense devotion to her husband's research contributed to the

Figure 4 Mrs. Andromache (Mary) Papanicolaou receiving the American Cancer Society of Philadelphia medal for her husband posthumously. Reprinted, with permission, from Charles C Thomas Publisher.

Figure 5 The Imperial Order of Saint Helen medal awarded to Lady Mary Papanicolaou, Miami. (http://www.new-byzantium.org/orderofs.html) (Accessed: July 07, 2014)[14].

successful development of Exfoliative Cytology as the major factor toward the conquest of uterine cancer.

She was the guest of honor at the 5th International Academy of Cytology congress in Miami, in 1974.

For her astonishing and selfless contributions to diagnostic medical science, she was also awarded the Imperial Order of Saint Helen award and thereafter called Lady Mary Papanicolaou.[14]

The following dedication was conveyed to her during that award ceremony in Miami (Fig. 5):

> *Lady Mary Papanicolaou*, spouse and close collaborator of *Dr. George Papanicolaou* (1883-1962), famous for his development of the "Pap Test," is awarded the Order of Saint Helen in honor of her important contribution to medical science as an assistant to her husband.

In Greek, the name *Andromache* means "a woman fighting alongside men," or, essentially, a woman being as strong as a warrior. Perhaps no other name could better champion her or her inner might. In her determination to support promising scientific work, in whichever way she could, Andromache Papanicolaou sacrificed much—denying herself the pleasures of motherhood, abandoning her family and friends—all in the spirit of their quest for the betterment of humanity. She was ultimately the central figure in the Pap test journey, and she managed very well all those matters within her grasp revolving around her, while never being out of touch with her responsibilities both in the laboratory and the homestead.

The author respects that she was a very intelligent, gentle, and dignified lady. And similar feelings are clearly borne out of commentaries from those that knew her.[1,2,11,12]

Lady Papanicolaou passed away in Miami, on October 14, 1982, at age 92.[15]

Her body was cremated with her ashes dispersed onto the Biscayne Bay in Florida; perhaps an unconscious request for her to be carried back to Greece with the restless oceanic currents.[13]

Her kindness, thoughtfulness, and devotion to her husband and their collective work shall survive her indefinitely through the Pap test, as well as through the women who have survived cervical cancer globally because of their scientific work.[16,17]

On behalf of humanity, the cytopathology community remains indebted to these pioneers and now celebrates 100 years since their epic revolutionary work at Cornell Medical College that produced the only systematic mass screening tool in the ongoing war against human cervical cancer based on cellular morphology.

Her odyssey is endless.

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