

After Office Hours

THE HISTORY OF THE PAPANICOLAOU SMEAR AND THE ODYSSEY OF GEORGE AND ANDROMACHE PAPANICOLAOU

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The Papanicolaou smear, a routine screening test for cancer of the uterine cervix, was reported in 1928, and its efficacy was proved by 1941. Since then, it has been used worldwide as a clinical tool for the early detection of cancer. Cancer of the cervix follows a predictable sequence. Precancerous changes, not visible to the naked eye, are detected readily in cells sampled by the Papanicolaou smear. The evolution from the precancerous stage to cancer is slow, and routine annual screening makes this a curable cancer and totally preventable disease. This is the story of an ambitious and brilliant man, George Papanicolaou, and his devoted wife, Andromache Mavroyenous, whose discovery of the screening test is now recognized as the most significant advance in the control of cancer in the 20th century. (*Obstet Gynecol* 1998;91:479–83. © 1998 by The American College of Obstetricians and Gynecologists.)

Beginnings

George Nikolas was born on May 13, 1883, the third child of Nikolas Papanicolaou and Maria Georgiou Kritsouta. He was raised with two sisters and a brother in Kymi, a small town overlooking the Aegean Sea on the island of Euboea, Greece. Dr. Nikolas Papanicolaou, physician and mayor of Kymi, was elected subsequently to the National Assembly. George, an exceptional and sentimental child, attended high school and university in Athens, where he studied literature, philosophy, languages, and music. He exhibited a talent in playing the violin. Because his older brother, Naso, studied law, George was persuaded by his father to

study medicine and carry on the family practice. He obtained his medical degree with honors in 1904 at 21 years of age. In October 1904, George was conscripted to the army and admitted to the academy for reserve officers. He was promoted to assistant surgeon and discharged in August 1906.

Postgraduate Education in Germany (1907–1910)

Upon completion of his military commitment, George was faced with the choice of practicing medicine in Kymi or continuing as a military physician, neither of which he found very appealing. After convincing his father to finance further studies, he arrived in Jena, Germany, in 1907 to study under Ernest Haeckel, an early supporter of Darwin's theory of evolution. His second semester was spent under August Weismann of Freiburg, a brilliant geneticist who speculated that inheritance is transmitted through sex cells. After his exposure to these two professors, he decided to devote his life to biological research and enrolled as a graduate student under Professor Richard Goldschmidt at the Zoological Institute in Munich, directed by Richard Hertwig. His thesis, assigned by Dr. Hertwig, was on sex differentiation and determination in the microorganism *Daphnia* (a genus of fresh-water crustaceans, called water fleas). By 1910, he had become a skilled microscopist, completed his experiments, received his doctor of philosophy degree, and returned to Greece. Research facilities at the University of Athens were primitive, and career opportunities were limited. Back in Kymi, everyone was anxious to see this well-educated physician practice his trade. What they saw instead, was a young doctor wandering aimlessly about the countryside.

On the ferry boat to Athens, he met Andromache, the daughter of Colonel Mavroyeni. Young Andromache had a vibrant personality, was well-educated, spoke French, and played the piano. George had met her previously through his sisters and had once treated her as a patient. Now, he was attracted immediately, and they were married on September 25, 1910, at her family home. Colonel Mavroyeni provided tickets to Europe, where George accepted a 1-year position at the Oceanographic Museum of Monaco. On July 19, 1911, he was selected as the physiologist for the scientific expedition led by Prince Albert of Monaco, on the oceanographic vessel *L'Hirondelle II*.

George's mother died in the early part of 1912, and the couple returned to Kymi. During the Balkan War of 1912, George served as a reservist and was promoted to lieutenant medical. In the army, he met many Greek-American volunteers, who encouraged him to immi-

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grate to America, where opportunities for a scientific career and research were unlimited.

Beginnings in America

On October 19, 1913, against the strong objections of both families, the couple arrived in New York with \$250. They had no particular place to go, were met by no one, and spoke no English. After securing a small apartment, they both found employment at Gimbel's department store, she sewing buttons for \$5 per week and he as a rug salesman. George supplemented his income by playing his beloved violin at restaurants and coffee shops and as a clerk at the Greek-language newspaper *Atlantis*.

After 3 weeks of selling rugs, he contacted Dr. TH Morgan of Columbia University, who recommended him as a technician to Dr. William Elser in the pathology and bacteriology department of the New York Hospital. Elser recognized George's superior ability and knowledge, and recommended him for a more challenging position at Cornell Medical College under Dr. Charles Stockard, chairman of the anatomy department. By September 1914, 1 year after their arrival, the Papanicolaou both were working at Cornell University, Andromache as her husband's assistant. Thus was formed the team that would become historic over the next 47 years.

Major Contributions

The Estrous Cycle of Guinea Pigs

Initially, Papanicolaou conducted Stockard's experiments on the effects of alcohol fumes on guinea pigs and their offspring. Realizing that extra guinea pigs were available, he received permission to conduct experiments on sex determination. To test his concept that X and Y chromosomes determined the sex of the offspring, he required guinea pig eggs at mitosis, just before ovulation. However, ovulation in guinea pigs could not be determined unless the animals were sacrificed. One morning, he woke up and scribbled down the following hypothesis: "The females of all higher animals have a periodic vaginal discharge; so lower animals such as these rodents, should also have one, but one probably too scanty to be evidenced externally."¹

The same morning on the way to work, he purchased at Tiemman's surgical supplies store a small nasal speculum to examine the vagina of his guinea pigs. He spread some of the vaginal debris on a glass slide and placed it under his microscope. By his own admission, "There were moments of real excitement when the

examinations of the first slides revealed an impressive wealth of diverse cell forms and a sequence of distinctive cytologic patterns."¹ That same evening, he observed similar cytologic patterns in the human, as the first Papanicolaou smear was performed on his wife. The cytologic patterns were correlated immediately to events in the ovary and changes in the uterus. In September 1917, they were published in the *American Journal of Anatomy* under the title "The Existence of a Typical Estrous Cycle in the Guinea Pig With a Study of Its Histological and Physiological Changes," authored by Stockard and Papanicolaou.²

The correlation of cytologic patterns to hormonal changes led to the discovery of many hormones by other investigators. Applying the same principle, Allen and Doisy in St. Louis isolated the ovarian estrogenic hormone in 1923, and Edgar Doisy received the Nobel Prize in 1943 for his work on the chemical structure of vitamin K. By 1919, Papanicolaou, at 36 years of age, was well known and had carved a permanent spot for himself within the scientific community. In 1920, Venizelos, Premier of Greece, offered him the chair of the zoology department at the University of Athens. Although tempted, he was well aware of the unfavorable conditions in Greece and did not accept.

Papanicolaou's guinea pig cytologic method proved to be a great diagnostic tool in a variety of conditions. He also studied cytologic vaginal patterns in the newborn, child, and menopausal women and in women with endocrine abnormalities. He also suggested hormonal replacement therapy in surgically castrated and menopausal women. "The sexual cycle in the human female as revealed by vaginal smears" was published in *The Journal of Anatomy* in 1933.⁴

New Cancer Diagnosis: The Papanicolaou Smear

In February 1925, Papanicolaou started a systematic study of vaginal smears volunteered by female workers of the New York Women's Hospital. After a chance encounter of a smear from a genital malignancy, he stated, "The first observation of cancer cells in the smear of the uterine cervix was one of the most thrilling experiences of my scientific career."¹ He recruited other women with cancer, confirmed his observations, and presented this new cancer diagnosis at the Third Race Betterment Conference in Battle Creek, Michigan, January 2-5, 1928.³ The *New York World* newspaper reported on January 5, 1928, "although Dr. Papanicolaou is not willing to predict how useful the new diagnostic method will be in the actual treatment of malignancy itself, it seems probable that it will prove valuable in determining cancer in the early stages of its growth

when it can be more easily fought and treated." Unfortunately, these prophetic words fell on deaf ears, and the discovery was received with little enthusiasm. The practical significance of the Papanicolaou smear as a screening test of cancer did not become apparent for another 10 years.

Dr. Joseph Hinsey, successor to Stockard as chair of the department of anatomy at Cornell Medical College, encouraged Papanicolaou to devote his time to developing his new cancer diagnosis. A clinical trial was organized in collaboration with Herbert F. Traut, a gynecologic pathologist at Cornell. Starting in October 1939, all women admitted to the gynecologic service of the New York Hospital had a routine vaginal smear interpreted by Papanicolaou. The findings were astounding. By use of the vaginal smear, a considerable number of asymptomatic and therefore unsuspected cases of uterine malignancy had been discovered, some of them in such an early stage of development that they were invisible to the unaided eye or were undemonstrable by the biopsy method. This landmark report, "The diagnostic value of vaginal smears in carcinoma of the uterus," was presented on March 11, 1941, and published in August 1941 in *The American Journal of Obstetrics and Gynecology*.⁵ The next decade was spent proving the value and efficacy of the Papanicolaou smear, teaching others the interpretation of the slides, and convincing the skeptics and nonbelievers. Papanicolaou summarized and published his observations in a comprehensive work, *Atlas of Exfoliative Cytology* in 1954.⁶

Return to Greece and Then to Miami

In 1957, after 44 years in the United States, the couple returned to Europe. Dr. Papanicolaou attended the First International Cytology Conference in Brussels and visited many centers and old friends in France and Germany. On the island of Corfu, Greece, the Papanicolaous were received by the royal family. The former royal residence, Achelion, was offered as a possible site for a research institute bearing Papanicolaou's name. While they were in Greece, negotiations began with the government and private sector for the establishment of a cytologic research institute. However, the proper location and adequate funding could not be secured, so they returned to the United States.

The opportunity for a research institute materialized when Papanicolaou was offered the directorship of the Cancer Research Institute of Miami. He accepted immediately, and in November 1961, the couple settled in DiLido Island, Miami Beach. He selected his staff for their competence and personality, and by January 1962,

research was on its way. The dedication of the institute was scheduled for May 1962. Unfortunately, on the morning of Monday, February 19, 1962, he woke up with chest pain and shortness of breath. A few hours later, he died at Jackson Memorial Hospital from a heart attack. His body was transported to New York, and he was buried beside his beloved niece, Maria Stamatiou, at the Presbyterian cemetery in the small town of Clinton, New Jersey.

Honors and Awards

Papanicolaou's contributions were acknowledged universally. He founded the science exfoliative cytology and authored 158 publications. He accepted membership to many faculties and societies and received a multitude of honors and degrees, including one from the University of Athens. He also was elected an honorary Fellow of the Academy of Athens, a rare honor indeed.^{7,8}

In 1960, he was nominated for the Nobel Prize in Physiology and Medicine. Of 120 submissions, 15 were judged to be worthy; his was ranked third. Stamps of approval, awards, and dedications continue posthumously to this day. On January 16, 1995, the Greek government released the 10,000 drachma bank note with Dr. Papanicolaou's picture.

On October 10, 1962, he received the United Nations award. Postage stamps of three nations have been dedicated to him and his work (Figure 1). The first lady of the United States, Rosalyn Carter, revealed the United States stamp on May 18, 1978, and presented it to Mrs. Papanicolaou at the White House. In addition, the Cornell Medical Center dedicated its Anatomy Library to Dr. Papanicolaou in November 1968, where a sapling from the Hippocratic maple tree, from the island of Cos, also was planted in his honor, in front of the Cornell Medical School, in 1978. Since then, the graduating class recites the Hippocratic oath under that tree. On October 18, 1979, a bust of Dr. Papanicolaou was unveiled in the foyer of the New York Hospital of Cornell Medical Center.

Andromache Mavroyenous-Mary Papanicolaou

It has been said that behind a great man there is always a great woman. *Andromache* means a woman fighting with men. No better name could describe Mrs. Papanicolaou. Whereas her great grandmother, Manto Mavroyenous, fought in 1821 to liberate Greece from the Ottoman Empire, Andromache labored continuously for the welfare and recognition of one man, Dr. Papanicolaou.^{9,10} After she agreed to his eccentric demands,

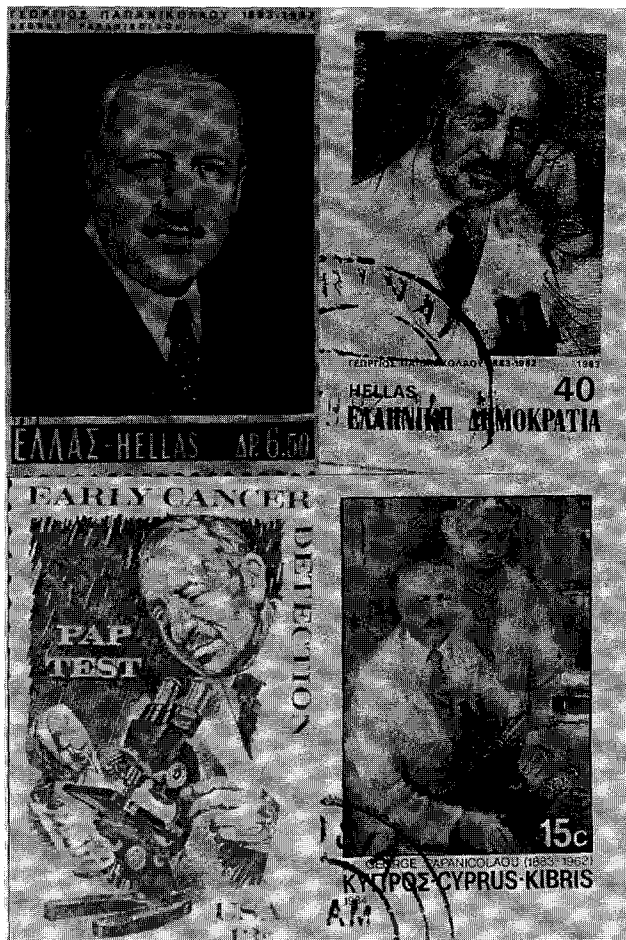


Figure 1. Four stamps have been issued by three nations in honor of the Papanicolaous and their work.

denying herself the joys of motherhood and accepting a hasty private wedding, she followed him to Europe in search of employment. While he worked in Monaco and upon the Hironnelle oceanographic vessel, she elected to go to Monastier near Lyon in France to take cooking classes.

Upon their return to Greece, still a young bride, she was left to stay with his family in Kymi while he returned to Europe for additional studies. Abandoning her family and friends, she followed him to New York and became the main breadwinner while he struggled to establish credentials and employment appropriate to his education. In the evenings, after a day's hard work, she would assume the role of cook, cleaner, loving wife, confidant, and manager of the family affairs. After they moved to Douglaston, Long Island, New York, in 1927, she was the gardener, the weekend chef of Greek delicacies, and the gracious hostess to his many distinguished visitors and friends.

As his technician, she became so proficient that she supervised and taught other cytotechnicians. When

Cornell would not allow a husband and wife to be employed in the same department, she volunteered her services. After the discovery of the exciting cytologic patterns in the vagina of guinea pigs, Mrs. Papanicolaou consented to become her husband's first experimental human subject. By his admission, she was a very special case with regular and uncomplicated cycles, studied over 20 years, and was the source of establishing normal cytologic patterns in women. Undoubtedly, Mrs. Papanicolaou must have been the most over-tested woman of all time. It is little wonder that Dr. Papanicolaou used to introduce her affectionately as "my wife and my victim."¹⁰ In recognition of her unselfish contributions, in March 1969, the American Cancer Society presented Mrs. Papanicolaou with a much deserved special award bearing the inscription, "To Mary Papanicolaou, Companion to Greatness."⁹ Andromache died October 13, 1982, in Miami Beach at 90 years of age. Her body was cremated, and the ashes were spread over Biscayne Bay in Florida. This final request might have been a subconscious wish to return someday to her beloved motherland by way of the Atlantic.

Epilogue

Because of George Papanicolaou, his birthplace, Kymi, has become a well-known place, but his final resting place is a flat tombstone overgrown by weeds in the little-known town of Clinton, New Jersey. His monumental contribution proved that cancer can be beaten. Until one of his disciples discovers a method to prevent cancer, the Papanicolaou screening test will remain one of the most powerful weapons against this disease. Those of us who looked upon him as a guiding star will always owe him our gratitude, and those women who were helped by his test owe him their lives.

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