



TRIBUTE

George Nicholas Papanicolaou: the unlikely story of an intellectual immigrant; one driven to contribute on a large stage; one who finally succeeded by scientifically inspiring numerous cooperating individuals and organizations

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Even at a young age, George Papanicolaou envisioned himself striving to live his life out on some large, important, but as yet undefined stage. After receiving his MD at 21, he resisted family pressure to take over his father's medical practice, earned a PhD in Germany, eloped with a woman who agreed to a life dedicated to science, and immigrated to America. At Cornell, he developed the vaginal smear technique to study endocrine cytology and then extended animal studies to humans, obtaining daily smears for years from his lab assistant wife. Around 1925, he recognized malignant cells in smears from asymptomatic women with cervical cancer. After the smear technique was initially rebuffed in 1928, he later collaborated with gynecologists, the American Cancer Society, the National Cancer Institute, and many others to develop the field of diagnostic cytopathology and medical history's first effective cancer screening test.

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The year 2014 marks the 100th anniversary of George N. Papanicolaou's employment (which began in September 1914) at Cornell Medical College as instructor in the Department of Anatomy. In this department over the subsequent 40 to 50 years Papanicolaou carried out his foundational work that established both the scientific discipline

of diagnostic cytopathology and medical history's first successful cancer screening test.¹⁻³ The extraordinarily unlikely story of his personal and professional journey to these achievements is inspiring, though sobering, for anyone who might seek to follow his footsteps in a research career. This tribute remembers Dr. Papanicolaou and highlights the most critical junctures in his life journey. In addition, nuances of his personality from the biographical publications now available present a portrait of the man and scientist. Another important aspect of his life career must have been the major regional and world events occurring in the background around him that were beyond his control. It is clear that these events had profound influences upon him and, in some instances, were unsurpassable restraints.

As the intellectually talented and personally ambitious son of a prominent physician and politically active resident in the Greek seaport town of Kymi, Papanicolaou left home to attend gymnasium (European high school) in Athens at age 11, was admitted to the University of Athens at age 15, and ultimately obtained a doctor of medicine diploma from the University of Athens in 1904 at the age of 21.^{4,5} He was a sentimental, bright young man who showed much potential. History reveals that Papanicolaou made fundamental decisions early in his childhood that he nurtured and followed throughout his life. Neither his ambitions nor his resolve to achieve them wavered.

Papanicolaou's first major extended struggle unfolded over the next decade as a result of his decision to resist strong family expectations that he return to Kymi, take over his father's medical practice, and accept an arranged marriage. We have had the privilege to obtain and read through his numerous and involved personal letters to his family, predominantly written in Greek. We have also translated the letters into English and thereafter gained insights into his thought processes, feelings, sensitivities, patience, and approaches. The portrait of Dr. Papanicolaou's character as alluded to in the wider scientific literature is completed from our study of his hand-written letters. We note acrimonious exchanges with his father who reluctantly supported his PhD graduate studies in Germany and who tried repeatedly to convince him to return home or at least, as an alternative, to accept a medical appointment in the Greek military. His letters also reveal how Papanicolaou envisioned himself even at a young age as striving to live his life out on some large, important, but as yet undefined stage.

After refusing an arranged marriage to the daughter of a wealthy Kymi merchant, in 1910 Papanicolaou eloped to marry Andromache "Mary" Mavroyeni, daughter of a Greek military officer and family that he had known since her teenage years. Mary had a stoic but passive personality and shared Papanicolaou's deep love of music; she accepted his marriage proposal for a life dedicated to science, without children, and possibly to be lived abroad.⁵ This, in retrospect, was perhaps the most fortunate of events in Papanicolaou's overall life and career, and it was a critical step, as Mary became his lifelong unpaid medical assistant and

"special case," donating daily samples from which Papanicolaou would teach himself normal female genital tract cytopathology.⁶ The remarkable story of the critical partnership between Papanicolaou and Mary is told in a separate article in this issue of *JASC*. In 1969, 7 years after Papanicolaou's death, the American Cancer Society formally acknowledged Mary's key role, recognizing her as "one who recognized greatness and served it."⁷

Papanicolaou immigrated to America in 1913 at the age of 30, after concluding that promising opportunities to pursue a basic science career in Greece or elsewhere in Europe did not exist for him. The couple courageously sailed into New York with no established employment and almost no money. Initially, they struggled to support themselves at a subsistence level while Papanicolaou sought to improve his English and find suitable employment as a scientist. Dr. Thomas Hunt Morgan of New York's Columbia University—who later won the Nobel Prize in Physiology or Medicine in 1933—had cited Papanicolaou's PhD thesis in a recently published book and helped Papanicolaou find basic employment at the New York Hospital, leading shortly thereafter to employment in a research position at Cornell. By 1917, Papanicolaou had developed the vaginal smear technique in guinea pigs as a morphologic method to follow the hormonal cycle and to identify the moment of ovulation.⁸ This technique was destined to become the Pap test, and it supported basic research by so many other Nobel prize-winning pioneers in endocrinology that Papanicolaou was referred to in 1932 in a major European journal as the "father of modern endocrinology."⁴ The meticulous attention to cellular morphologic detail reported in his beautiful older publications stands out as a testimonial to his astuteness following careful scientific observation.

In 1920 Papanicolaou began to extend these observations to humans, for years studying daily specimens collected from his laboratory assistant, Andromache.⁶ In the process, he gradually perfected the Papanicolaou stain and taught himself the fundamentals of human cytologic anatomy.³ This prepared him for the unexpected finding of cancer cells in a vaginal smear of a cervical cancer patient, which he would later recall as "one of the most thrilling experiences of my scientific career."^{1,5}

Papanicolaou's introductory presentation of his early observations on this new method for cancer diagnosis unfortunately took place at an ill-suited meeting of the American Eugenics Society, due to departmental chairman Dr. Charles Stockard's active involvement in this society. Given the dark history of the American Eugenics movement,⁹ one can only wonder whether this initial scientific platform might have been a subtle factor in Papanicolaou's being repeatedly denied the Nobel Prize. Papanicolaou's January 1928 presentation at the "Third Race Betterment Conference"¹⁰ almost ended his pursuit of this new diagnostic method, as pathologists argued assertively that the accessibility of the cervix to biopsy completely precluded

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