

George Nicholas Papanicolaou

May 13, 1883 — February 19, 1962

A scientific career of the first magnitude ended on February 19, 1962, with the sudden death of George Papanicolaou at age 78 in Miami, where he had gone only three months before to become Director of the Papanicolaou Cancer Research Institute. A quiet, gentle man, entirely devoted to research, had conceived, forty-six years before, the cytology of the vaginal smear as an accurate reflection of the cyclical events of estrus in laboratory animals and women, a conception soon to prove fundamental in the subsequent rapid developments in female endocrinology. A scientist, persisting always in the conviction that a microscopic study of exfoliated epithelial cells could reveal important processes in the intact mammalian subject, had conceived nearly forty years before, and nearly twenty years before any of his contemporaries, a simple and reliable method of recognizing early human cancer. The thread of his long productive effort is clearly followed from his doctoral thesis on sex differentiation in 1910 to the publication of the second supplement to his now classic *Atlas of Exfoliative Cytology* in 1960.

George Nicholas Papanicolaou was born on the Isle of Euboea, Greece, May 13, 1883, and at age fifteen began a didactic study of medicine at the University of Athens. Upon graduation in 1904 he was expected to follow in the respected and remunerative footsteps of his father in the practice of medicine. Nicholas Papanicolaou had little sympathy for an academic career in philosophy or science, which his son proposed, and was never to learn of his son's later fame in science and medicine. The son prevailed and was permitted to continue his studies abroad. Disenchanted with his study of philosophy in Vienna but with a newly acquired spark of interest in experimental biology, Papanicolaou enrolled as a graduate student in Hertig's Institute for Experimental Biology at the University of Munich under the direct supervision of Richard Goldschmidt. This was the exciting time of the recognition of chromosomes as bearers of Mendelian units of heredity, and Goldschmidt was achieving recognition in a degree similar to that of Thomas Hunt Morgan in this country. Papanicolaou's interests were directed to sex differentiation and sex determination in daphnians. During these years in Munich, Papanicolaou became acquainted with fellow students Frederick Gudernatsch and Robert Chambers and barely missed meeting Charles Stockard, with all of whom he was to be associated a few years later in the Department of Anatomy at Cornell University Medical College.

In 1910 with a Ph.D. from the University of Munich, Papanicolaou returned home and married a friend of his boyhood, Mary Mavroyeni, who was to remain his staunch support throughout his life and who even yet carries

on his research in Miami. On their honeymoon to Marseille, Papanicolaou by chance was offered a position as physiologist at the Oceanographic Institute of Monaco, which he accepted. But a year later, with the outbreak of the Balkan War, he was called to military service as a medical officer. In these campaigns of 1912-1913, Papanicolaou became enraptured with the United States through descriptions by American medical officers serving as volunteers in the Greek Army, and he decided then to pursue his scientific career in America. In the autumn of 1913, Dr. and Mrs. Papanicolaou arrived in New York with only the legally required \$250 and without friends or introductions. Aware of the reference of his Munich doctoral thesis in Morgan's just published *Heredity and Sex*, Papanicolaou called on Morgan at Columbia University and was found a part-time job in the Department of Pathology and Bacteriology of the New York Hospital. A year later he obtained a full-time research position at Cornell Medical College in the newly created Department of Anatomy under Professor Charles Stockard, and in this department Papanicolaou was to pursue his interests for forty-seven years, until a few months before his death.

Stockard's research involved the extensive breeding of guinea pigs and a need to know the time of ovulation. To Papanicolaou it became apparent how little was known of the estrus cycle in any mammal, including man. In 1917, he was able to publish with Stockard a definitive description of the histologic changes in the estrus cycle of the guinea pig, in which was established the correlation of the cytology of the vaginal smear with the ovarian and uterine cycles. Within a few years the method was generally accepted as valid and essential to the experimental approach to mechanisms underlying estrus, and it had been extended to other laboratory animals in other departments of anatomy by Corner, Long and Evans and Allen just prior to the discovery of the hormonal nature of follicular fluid by Allen and Doisy.

After 1923, in extending the correlation of the vaginal smear cytology with the ovarian cycle in pregnant and nonpregnant women, and in taking care to include specimens from patients with endocrine and genito-urinary disease, Papanicolaou began to recognize cells from carcinoma of the uterus and in 1928 published this finding. Neither at home nor abroad did he receive encouragement or acceptance, and he was not to resume this research until a decade later, with the encouragement of Stockard's successor, Joseph Hinsey, and the effective collaboration with the gynecologist Herbert Traut. A series of decisive publications with Traut followed, culminating in their monograph *Diagnosis of Uterine Cancer by the Vaginal Smear* in 1943.

In the succeeding decade the diagnostic technique was extended to the recognition of cancer of the respiratory, urinary, and upper gastrointestinal tracts and breast through the cytology of exfoliated cells. In the diagnosis of cancer, exfoliative cytology began to receive worldwide recognition. Pathologists and technologists from

more than forty foreign countries came to learn its application at first with Dr. Papanicolaou, later in a training program under his associate, John Seybolt. Honors and invitations poured in on Papanicolaou—Borden, Amory, Lesker awards to name a few; the highest decoration by the King of Greece; honorary degrees in three universities, honorary fellowships in every conceivably relevant scientific or medical society. But Papanicolaou could nearly always be found alone, or with one associate, in his laboratory bent over his microscope. Striving largely successfully to keep himself free of all but the most puzzling individual diagnostic problems, torn between choosing to pursue his research toward developing new applications of exfoliative cytology in cancer diagnosis or toward attempting to reveal new reflections of physiologic processes in exfoliative cytology, he chose the former and spent much of this remaining time in the compilation of his magnificent *Atlas*. Although nearly two decades of active research remained to him and nearly two-thirds of his publications were yet to appear, the second of his two great contributions had now been made.

Statutory retirement was nominally recognized in 1948 but made no real change in Papanicolaou's laboratory.

Never enthusiastic or very effective as a teacher, he was enabled by the College in his forty-seven year association with it to pursue his research with minimal teaching responsibility. Partly as a consequence, and despite the fact that hundreds of technologists trained under his supervision and dozens of senior investigators collaborated with him, he developed very few young men to succeed him in his research.

In later years, facing several opportunities from outside the University, he began to dream of an institute for research and training in exfoliative cytology, and after long consideration and in the face of the expressed hopes of his many friends and associates at Cornell that he continue in his established laboratory and home, he finally in 1961 decided to accept the directorship of the Papanicolaou Cancer Research Institute of Miami. Although many at Cornell feared such a move might this late in life overwhelm him, none but could admire his great courage and glint of determination as he described his plans for the new Institute.

Surely the institute Dr. Papanicolaou envisioned will develop and contribute significantly, and surely young scientists will follow along the path which Dr. Papanicolaou traveled so far by the most careful and persistent microscopic observation and along which path he could, even at age 78, see so far.

Roy C. Swan