

SPECIAL ARTICLE

George N. Papanicolaou (1883-1962): Fifty years after the death of a great doctor, scientist and humanitarian

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Summary

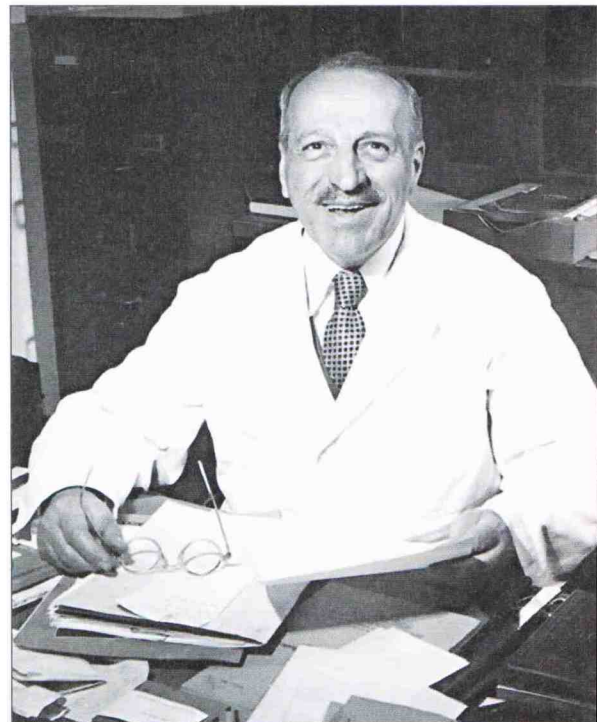
Fifty years have passed since the death of Dr George Nicholas Papanicolaou, who was born in Kyme at the island of Euboea in Greece in 1883 and became known for his innovative revolutionary invention of the Pap smear test performed at the Cornell University Medical College in the USA. To date, even after the introduction of HPV vaccination into the clinical practice, Dr George Papanicolaou's method

remains an essential component of the prevention strategy against cancer and has resulted in a 70% decrease in cervical cancer mortality over the last 60 years. This article, which presents briefly his biography, is dedicated to him on the occasion of the 50th anniversary of his death.

Key words: George Papanicolaou, the Pap smear test, 50 years after his death

Introduction

Fifty years after the death of Dr George Nicholas Papanicolaou, a great Greek doctor, scientist and humanitarian, the invention of the Pap smear test remains a unique tool for the early detection of cervical cancer. Dr George Papanicolaou, who was entirely devoted to research, recognized the presence of abnormal cancer cells, while studying microscopic slides of exfoliated epithelial cells in body fluids of laboratory animals and humans. His observations led to the famous Pap smear test that bears the first syllable of his last name. The introduction of this innovative revolutionary method for early cancer detection into the clinical practice resulted in a 70% decrease in cervical cancer deaths over the last 60 years. To date, the Pap smear test, which is still reliable, has saved millions of lives of women around the world by early detection and prevention of cervical cancer, a leading cause of deaths among women worldwide. The research that Dr George Papanicolaou pursued during his life-long career established the field of Exfoliate Cytology and currently he is recognized as "the father" of modern Cytology. With his magnificent "Atlas of Exfoliative Cytology" published in 1960, he



George N. Papanicolaou, MD (Kyme, Greece, 1883 - Miami, U.S.A., 1962).

created the foundation of the modern medical specialty of Cytopathology. Dr George Papanicolaou is also remembered for his research devoted to the physiology of reproduction and the study of cell alterations during the menstrual cycle.

This article, which reviews the life and achievements of Dr George Papanicolaou, is dedicated to him on the occasion of the 50th anniversary of his death.

His birth and childhood

Dr George Nicholas Papanicolaou was born in Kyme, a seaside village on the eastern slopes of the Greek Island of Euboea in May 13, 1883. He was the third child of Maria G. Kritsouta and Nicholas A. Papanicolaou, who was a well-known local general practitioner, senator and mayor of the municipality of Kyme. As a young boy George spent all his early childhood with his two sisters and his brother in Kyme, where he loved the olive-tree nature of his island and the endless horizon of the Aegean Sea [1]. At the age of 11, he moved to Athens, where he continued his studies in high school.

Undergraduate and postgraduate studies in Europe

He studied Medicine at the University of Athens School of Medicine, where he enrolled in 1898. After his graduation in 1904 with honors, he performed his compulsory military service at the Hellenic army for two years. Although he was expected to follow in the respected carrier footsteps of his father Nicholas Papanicolaou, Dr George Papanicolaou decided to continue his post-graduate studies. In the spring of 1907, he initially moved to Jena in Germany, where he began his postgraduate studies under Professor Ernst Haeckel, one of Europe's greatest early proponents of Darwinism and then to Freiburg under the tutelage of Professor August Weismann, a brilliant early geneticist. One year later, he enrolled as a graduate student in "Hertig's Institute for Experimental Biology" at the University of Munich under the direct supervision of Professor Richard Goldschmidt. In 1910 Dr George Papanicolaou earned his PhD in Zoology for his thesis entitled "Sex differentiation of the daphnia", which was published in German [2].

His marriage and his voyage in Europe

In September 15, 1910 he married Andromache

Mavroyeni, later known as Mary Papanicolaou, who was to remain his staunch supporter throughout his life. Shortly after their wedding, Dr George Papanicolaou visited the famous Oceanographic Museum in Monaco, where he was briefly employed from January 1911. In July 1911, he sailed with Prince Albert I of Monaco aboard the oceanographic vessel, L'Hirondelle II on a marine research expedition in the Mediterranean Sea and Atlantic Ocean, joining as a physiologist. In 1912, he was re-called to military service and he participated in the Balkan Wars as a lieutenant medical officer in the Hellenic army medical corps. During the war, he met many Greek-American volunteers, who encouraged him to immigrate to the USA where the opportunities for a scientific career and research were unlimited [1].

Immigration to the USA

Looking for an opportunity for biological and medical research, in October 19, 1913 Dr George Papanicolaou and his wife Mary arrived in New York with only the legally required \$250. Unable to find work, he obtained a job as a rug salesman in Gimbel's department store. He quit this job on his second day, too embarrassed to show some rugs to a woman he had met during his first-class passage with Mary to the USA [1]. Initially he found a part-time job in the Department of Pathology and Bacteriology of the New York Hospital after his recommendation by Dr Thomas Hunt Morgan of Columbia University. A year later he obtained a full-time research position at the Cornell University Medical College in the newly created Department of Anatomy under Professor Charles Stockard and in this Department Dr George Papanicolaou was to pursue his interests for 47 years, until a few months before his death.

Early research at Cornell University Medical College

Dr George Papanicolaou began working on Professor Charles Stockard's experiments on the effects of alcohol fumes on guinea pigs and their offspring. He also received permission to conduct experiments on their gender differentiation studying microscope slides of their vaginal secretions. His initial research involved the recurring cytological changes over a 15 to 16-day cycle in their vaginal discharge. As his work progressed, he made daily observations of their vaginal smears so that their microscopic changes could be

assessed. He discovered that the oestrous cycle occurred for 24 hours every 15 or 16 days and he correlated the smear pattern with changes in the ovary and uterus. His further experiments required obtaining the ova of female guinea pigs at a precise stage of development near ovulation, which he could determine based on the pattern of their vaginal smear. In 1915, he published his first paper in *Science* entitled "Sex determination and sex control in guinea pigs" [3]. This paper was followed in 1917 with two more detailed reports, published in *Science* [4] and in the *American Journal of Anatomy* [5] giving a more definitive description of the histologic changes in the oestrous cycle of the guinea pig.

Describing the changes in forms of the epithelial cells according to the animal's oestrous or menstrual cycle, he managed to study the menstrual cycles and sex hormones of other laboratory animals [6,7]. By correlating these changes with the ovarian and uterine cycles, he described a technique that in time became standard for measuring the sexual cycles in a variety of species. Within a few years this method was generally accepted as valid and essential to the experimental approach to mechanisms underlying oestrous and it was also extended to other laboratory animals.

The challenge to return

In 1920, the Prime Minister of Greece, Eleftherios Venizelos, offered him the chair of the Zoology department at the University of Athens [1]. Although tempted to return to his home country, he was well aware of the unfavorable conditions in Greece and did not accept.

The initial description of the Pap smear test

After 1923, Dr George Papanicolaou extended the correlation of the vaginal smear cytology with the ovarian cycle in pregnant and non-pregnant women and he managed to include specimens from patients with endocrine and genitourinary diseases. In continuing his work on human specimens with cervical cancer, Dr George Papanicolaou discovered that women with cervical cancer exhibited "abnormal cells, with enlarged, deformed or hyperchromatic nuclei". He termed it as "one of the most thrilling experiences in my scientific career" [1]. In 1928, at the Third Race Betterment Conference in Battle Creek in Michigan, Dr George Papanicolaou presented his findings and he introduced his low-cost, easily performed screening test for early detection of cancerous and precancerous

cells [8]. However, his report received little scientific notice and was met with skepticism. Dr George Papanicolaou was being treated as a "story-teller" by the medical nomenclature of that time and his technique was considered as an unnecessary addition to existing diagnostic methods for cervical cancer [1]. Over the next decade, Dr George Papanicolaou paid little attention to his research in this area.

The Pap smear test

In 1939, at the encouragement of a colleague, Dr Herbert Traut, a gynecologist from the Department of Obstetrics and Gynecology, who appreciated the importance of his previous research, Dr George Papanicolaou continued his work in this field and was allowed to devote full time to his research. To validate the diagnostic potential of the vaginal smear, Dr Herbert Traut enrolled women admitted to the gynecologic service of the New York Hospital. Each woman underwent a smear that Dr George Papanicolaou interpreted. Based on Dr George Papanicolaou observations, it was well established how lesions could be detected in their incipient, preinvasive phase at a turning point in the management of cervical cancer.

In March 11, 1941, Dr George Papanicolaou and Dr Herbert Traut published their findings in their paper entitled "The diagnostic value of vaginal smears in carcinoma of the uterus" [9]. This was followed 2 years later in 1943, by an illustrated monograph entitled "Diagnoses of uterine cancer by the vaginal smear" based on a study of over 3,000 cases [10]. In this monograph, Dr George Papanicolaou and Dr Herbert Traut presented the preparation of vaginal and cervical smears, physiologic cytologic changes during the menstrual cycle, the effects of various pathological conditions and the changes seen in the presence of cancer of the cervix and of the endometrium. They also highlighted their conclusive findings that showed smears of vaginal fluid could indicate cervical and uterine cancer before symptoms appear. At this time the medical community took notice of this "new cancer diagnosis" and the Pap smear test methodology won acceptance. A series of decisive publications followed [11-13] and the Pap smear test soon became widely accepted as a routine screening technique worldwide.

From 1947, Dr George Papanicolaou as a Professor of Anatomy, continued his research trying to perfect his cytological method. He also trained others in the cytological method in courses that ranged from a few weeks to 6 months. Over the following years, Dr George Papanicolaou extended his technique to the

respiratory [14,15], urinary [16-19] and gastrointestinal tracts [20-23], the breast [24,25] and the pancreas [26,27].

His Atlas of Exfoliative Cytology

In 1954, Dr George Papanicolaou published the "Atlas of Exfoliative Cytology" [28], a comprehensive work that featured his observations with supplements in 1957 and 1960. With this memorable work, Dr George Papanicolaou created the foundation of the modern medical specialty of Cytopathology. Due to Dr George Papanicolaou's efforts, Exfoliated Cytology attracted worldwide attention.

The end of his life

Toward the end of his life he dreamed of an institute for Exfoliative Cytology, desiring a less constrained research environment, where future scientists and technicians could be trained. In 1957, after he retired as the Professor of Clinical Anatomy at the Cornell University Medical College, Dr George Papanicolaou and his wife Mary visited Europe, where he attended the First International Cytology Conference in Brussels. He also visited Greece to pursue the possibility of establishing a cancer research institute in his home country, unsuccessfully. In 1961 he moved to Miami, Florida, to develop the Papanicolaou Cancer Research Institute at the University of Miami. However, only a few months after moving to Florida, in February 1962, Dr George Papanicolaou died of a myocardial infarction at the age of 79, prior to its opening.

Acceptance and worldwide appreciation of his contribution

Dr George Papanicolaou authored four books and over 150 publications [29]. Throughout his life, he received numerous awards and honors, including the Borden award of the Association of Medical Colleges in 1940, the Albert Lasker Award for Clinical Medical Research of the Public Health Association in 1950 and the honor medal from the American Cancer Society in 1952. In 1956, he became an honorary Fellow of the American Society of Clinical Pathologists and in 1957 he was elected as an honorary Fellow of the Academy of Athens. In 1960, he was nominated for the Nobel Prize in Physiology and Medicine and he was awarded the United Nations Prize in 1962 [1,29].

Dr George Papanicolaou, a great doctor, scientist and humanitarian

Dr George Papanicolaou was a great doctor, scientist and humanitarian, who was entirely devoted to research [1,29,30]. Throughout his career, his work habits and his character remained constant. He was a dedicated scientist working 14 hours a day and 6 or 7 days a week in his laboratories at Cornell and at home with no vacations for years. It was not until 1957, that he visited for the first and last time his birthplace Greece following his immigration to the United States in 1913. During his scientific career, he was chiefly assisted by his wife Mary, his companion throughout his life. He operated with great care and thoroughness and he remained a courtly man who treated his achievements lightly.

His life-saving test, the Pap smear test, a unique method for the early detection of cervical abnormalities prior to the development of invasive cervical cancer, became famous worldwide [30]. With the introduction of the Pap smear test into the national cervical screening programs, the incidence and mortality of cervical cancer has been drastically reduced over the last 60 years [31]. Due to this remarkable success, the Pap smear test is now recognized as the most significant advancement in the control of cancer in the 20th century.

During the last decade, new technologies have aimed to replace microscopic screening with molecular human papillomavirus (HPV) DNA testing [32]. HPV DNA testing has been proposed as a routine screening method for the general population. However, screening limitations, test sensitivity and specificity, access and cost-effectiveness of the HPV DNA test have highlighted the value of the traditional Pap smear test and the newer liquid-based cytology. Recently, in 2008 the introduction of the prophylactic vaccines against HPV 16 and 18 into the clinical practice was a major milestone in cervical cancer prevention [33]. These vaccines protect against the infection of certain oncogenic HPV types and therefore prevent the development of cervical dysplasia, precancerous lesions and cervical cancer. However, routine cervical cancer vaccination in adolescent girls offers protection only against the oncogenic types included into the vaccines and this proposes the need of continuing screening practice for HPV-vaccinated women [34]. Organized vaccination and screening programs with good record keeping are necessary to optimize the future control of cervical cancer. In this new period, fifty years after the death of Dr George Papanicolaou, the Pap smear test remains the most successful cancer screening test yet developed in the entire history of medicine and the answer to the question "Is it time to give up the Pap smear test?" remains negative [32].

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