

George N. Papanicolaou (1883-1962), an exceptional human, scientist and academic teacher: An interview with Dr Neda Voutsas-Perdiki

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Abstract. Dr Neda Voutsas-Perdiki, former Director of Exfoliative Cytology at the University of Florida (Florida, USA), talks about her academic teacher Dr George N. Papanicolaou, referred to as the 'Father of Exfoliative Cytology', and his wife Mache, known as Mary Papanicolaou. According to Dr Voutsas-Perdiki, Dr Papanicolaou was an exceptional teacher and a unique humanitarian in modern medical history. The secret of his scientific success was hard work, dedication, love of research, faith and the courage he gained from his wife and colleagues. According to Dr Voutsas-Perdiki, although Dr Papanicolaou was nominated for the Nobel Prize for at least 5 times, the reason for not receiving it remains unclear. His research was mainly clinical and not purely experimental, she adds. The official launch of her recently published book about Dr Papanicolaou entitled 'Dr George and Mache-Mary Papanicolaou - As I knew them' was held on March 1st, 2017 at the 'Benaki' Museum in Athens, Greece.

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1. Introduction

Born in Kyme on the Island of Euboea in Greece on May 13th, 1883, Dr George N. Papanicolaou (Kyme, Island of Euboea, Greece, 1883 - Miami, Florida, USA, 1962), referred to as the 'Father of Exfoliative Cytology', was undoubtedly an outstanding doctor, scientist and humanitarian in modern medical history (1-3). He studied Medicine at the University of Athens,

Greece, where he received his MD in 1904 and he completed his PhD at the University of Munich in Germany in 1910. On October 19th, 1913, he moved to New York accompanied by his wife, Mache, known as Mary Papanicolaou (Kyme, Island of Euboea, Greece, 1890 - Miami, Florida, USA, 1982), and one year later, in September 1914, he joined the Cornell University Medical College's Department of Anatomy in New York, where he performed his scientific work for the rest of his life. In 1915, he published his first article in 'Science' on sex determination in guinea pigs (2,4). After 1923, Dr Papanicolaou clarified the correlation of the vaginal smear cytology with the ovarian cycle in pregnant and non-pregnant women and discovered that women with cervical cancer exhibited 'abnormal cells, with enlarged, deformed or hyperchromatic nuclei' (1). In January 1928, he presented his findings, entitled as 'New Cancer Diagnosis', at the Third Race Betterment Conference in Battle Creek, Michigan, where he introduced his low-cost, easily performed screening test for early detection of cancerous and precancerous cells. However, this potential medical breakthrough was initially met with skepticism and resistance from the scientific community at that time, and his technique was initially considered an unnecessary addition to the existing diagnostic methods for cervical cancer (1).

Almost 10 years later, in 1939, at the encouragement of the gynaecologist Dr Herbert Traut, Dr Papanicolaou continued his work in this field and on March 11th, 1941, Papanicolaou and Traut published their findings in their paper entitled 'The diagnostic value of vaginal smears in carcinoma of the uterus' (5). At this time, the Pap smear-test technique won acceptance and soon became widely accepted as a routine screening methodology, worldwide. The Pap smear-test as a cytological test detecting early squamous intraepithelial lesions (SILs) remains a unique precancerous screening test in the entire history of Medicine. Although Dr Papanicolaou ignored the existence of human papillomavirus (HPV), his intervention was definitely a significant step in the field of HPV Virology (3,6,7). His life has been characterised by his phrase: 'My ideal is not to become rich, or to be happy, but to work, to act, to create, to do something worthy of an ethical and strong man' (8). His saying 'I live to serve life' (8) has been inscribed on his bronze statue situated on his home island, Euboea, close to the new Evripos Bridge spanning 700 m between the Island of Euboea and the mainland Greece.

In 2016, one of Dr Papanicolaou's students, Dr Neda Voutsas-Perdiki, former Director of Exfoliative Cytology at the

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University of Florida (Florida, USA), published her book (Fig. 1) entitled 'Dr George and Mache-Mary Papanicolaou - As I knew them' (9). Born on May 7th, 1930 in Mytilene on the Island of Lesbos, Greece, Dr Voutsas-Perdiki studied Medicine at the University of Athens School of Medicine (1949-1955). She specialised in Anatomical Pathology and Cytology in Greece, as well as in the USA, where she had the chance to attend as a Research Associate the Laboratory of Dr Papanicolaou at the Cornell University Medical College in the 'New York' Hospital from July 1st, 1958 to June 30th, 1959 (Fig. 2). She stayed in the USA from 1956 until 1964, where she worked as a Cytologist in the 'Mass Memorial' Hospital and 'Salem' Hospital of the Boston University, in the 'Papanicolaou' Research Laboratory at the Cornell University Medical College in New York, the 'Baptist Memorial' Hospital and the 'J. Hillis Miller' Health Centre of the University of Florida in Florida. She was the founder and the Director of the Department of Exfoliative Cytology at the University of Florida. After her return to Greece, she worked as a Director of Exfoliative Cytology in 'Evangelismos' Hospital, Hellenic Red Cross, Thoracic Diseases General Hospital 'Sotiria' for more than 10 years and 'Mitera' Hospital in Athens, Greece (9). Her book was edited by the Medical Council of Athens (MCA) and was prefaced by the President of the MCA George Patoulis, MD. The official launch of her book was held on March 1st, 2017 at the 'Benaki' Museum in Athens, Greece, under the auspices of the President of the Hellenic Republic, Mr Prokopios Pavlopoulos. In the context of the 3rd Workshop on Paediatric Virology, which will be held in October 7th, 2017 in Athens, Greece (10), Dr Neda Voutsas-Perdiki will announce the awards recipients of the meeting.

2. Questions and Answers

Question: Dr Neda Voutsas-Perdiki, first of all, thank you for agreeing to talk to us about your academic teacher Dr George N. Papanicolaou. You attended his Laboratory at the Cornell University Medical College in the USA from July 1st, 1958 to June 30th, 1959. During this period, his Pap smear-test was recognised and accepted by the worldwide scientific community. Moreover, his new scientific field of the Exfoliative Cytology had already been officially introduced. What was the secret of Dr George N. Papanicolaou's scientific success?

Answer: I met Dr George N. Papanicolaou, for the first time in 1958, having been referred by my Professor of Pathology in Boston Sheldon Sommers and I worked as a Research Associate in his Laboratory at the Cornell University Medical College in the 'New York' Hospital. During this period, the Pap smear-test and Exfoliative Cytology were recognised and accepted by the worldwide scientific community. He was my mentor. He was an ethical and an honest and great man. He was very simple in his behaviour. He was as simple and as great as his method, the Pap smear-test. He was indeed an exceptional teacher and a unique humanitarian of modern medical history. His secret was hard work, dedication, love of research, faith and the courage he gained from his wife, Mache, and his colleagues.

Question: From your USA experience, as well as your collaboration with Dr George N. Papanicolaou, what were the main

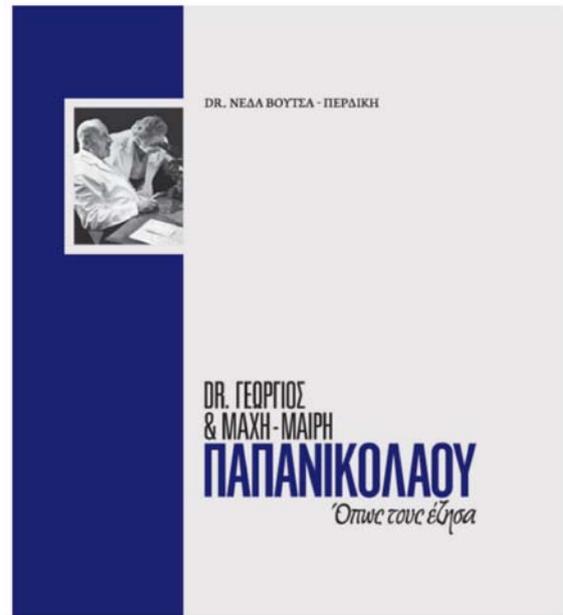


Figure 1. The cover of the book of Dr Neda Voutsas-Perdiki entitled 'Dr George and Mache-Mary Papanicolaou - As I knew them' published by the Medical Council of Athens, Greece in 2016.



Figure 2. Dr Neda Voutsas-Perdiki as a Research Associate at the 'Papanicolaou' Research Laboratory of the Cornell University Medical College in New York (New York, NY, USA) in 1959.

reasons that he did not manage to receive the Nobel Prize in 1959? During that year you were working in his Laboratory and we can thus assume that you discussed this with him.

Answer: Although he was nominated for the Nobel Prize for at least 5 times, namely in 1948, 1949, 1951, 1953 and 1959, he did not manage to receive it. The reason remains unclear, although it may be because his research was mainly clinical and not purely experimental. The Professor of Anatomy, Donal

Sheehan, and the Professor of Obstetrics and Gynaecology, Walter Dannreuther of 'New York' University, were the first Nobel Prize nominators of Dr Papanicolaou in 1948. Eleven years later, in 1959, he came close to receiving the prize; however, the person, who supported Dr Papanicolaou's nomination for the Nobel Prize, died. This person was Professor Axel Westman, Professor of Obstetrics and Gynaecology at the Karolinska Institute in Sweden. Thus, Dr Papanicolaou lost his principal supporter before the final decision; he was extremely unlucky. It was as a matter of bad luck and definitely not a matter of failure. In 1959, the Nobel Prize in Physiology or Medicine was awarded to Dr Severo Ochoa from 'New York' University School of Medicine and to the New Yorker Dr Arthur Kornberg of the National Institutes of Health for their very interesting discovery of the mechanisms involved in the synthesis of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). I remember that that year, Dr Papanicolaou accepted the choice of the Nobel Prize committee and said that the scientists, who finally received the Nobel Prize, Dr Ochoa and Dr Kornberg, were worthy of getting it. He, as well Mache in the following years, did not express any disappointment or dissatisfaction on this event.

Question: According to a local newspaper of Kyme, on Sunday, October 19th, 1975, 70 Greek doctors, who had been trained in the USA, knelt in front of his statue in the main square of Kyme on his home Island of Euboea. Two weeks later, on the 3rd of November 1975, you mentioned the following in one of your letters to Mary Papanicolaou: 'Last weekend we visited Kyme to pray in front of Dr Pap's statue'. Interestingly, you used the term 'to pray'. How 'holy' was he for you?

Answer: On October 19th, 1975, seventy Greek medical doctors, who had been trained in the USA, went to Kyme, on the Island of Euboea and prayed in front of the statue of Dr Papanicolaou in the main square of Kyme. I was one of them. I believe that this was an expression of gratitude and blessings to our Great Benefactor. Dr Papanicolaou was 'holy' for all of us. And he is still 'holy' for all medical scientists as well as for all the women in the world, who have benefited from his method.

Question: We read in your book your very interesting correspondence with Dr George Papanicolaou, who supported your presence in the USA giving you advice on your career. How significant was his role as a mentor to young scientists at that time?

Answer: Dr Papanicolaou's correspondence with me, which has been included in my book, his useful advice, the valuable time that he spent in our meetings and his supportive recommendations are a proof of the support he gave as a mentor to the young scientists at that time. His help was continuous and invaluable.

Question: A really touching detail in your book is the way that you describe his 'nostalgia' for his country and his home place. "It was spring, and we were sitting in the garden of his house in Douglaston in New York. Flowers, plants, blooming trees, fragrances were everywhere. Appreciative of these natural creations, he sighed: 'If everything was the same as in my country, I wouldn't feel any nostalgia - after almost 40 years - for the magic of the Greek spring'". How strong was his 'nostalgia' for his homeland?

Answer: His sense of 'nostalgia' for Greece was very great. Once, when we were sitting outside in the garden of his beautiful house in Douglaston, he was talking of the magic of the Greek spring in the homeland of his childhood, the Island of Euboea. He frequently referred to the Easter season, especially to the mystagogy of Maundy Thursday and Good Friday and the byzantine melodies of the church. In Kyme, as a child, he used to sing at the church those days himself. For this reason, he used to spend his Easter holidays with his nephew Vaggelis Stamatiou and his family, who lived close to Dr Papanicolaou's house in Douglaston. One Easter, Dr Papanicolaou refused to go to them, as he had too much work to do. So, they proposed to him to move his microscope to their garden; Dr Papanicolaou gave his consent to their proposal and finally he came.

Question: In 1957, after 44 years of continuous work, he managed to re-visit Greece for the first and last time.

Answer: Yes. He did it. This trip was the dream of his whole life. This was his only trip. 'The only trip of his life' as Georgios Vizenos, a Greek writer and poet of the 19th century, says. The final destination of this trip was Kyme, where he has spent his childhood and adolescence. Before arriving at his village, he stopped to face the endless horizon of the deeply blue sunny Aegean Sea. On the second day in Kyme, he asked to see all the places of his childhood. He woke up early in the morning and he asked to visit by boat the rocky northern coast of Kyme. That morning, it was extremely windy and they advised him not to do it. He persisted, until by wooden sloop they started their boating. He managed to see the pine forest beach of 'Soutsini', where the leper colony was located, where, as a child, he had frequently gone to offer food and clothes to the residents. He asked the captain to continue beyond the cape of 'Kavos' to the small island of 'Chille', the place visited by Achilles, the hero of the Greek Mythology, before his trip to the Island of Skyros and Troy. The waves were becoming bigger and bigger. The north wind was becoming stronger and stronger. It was only when the captain of the sloop explained to him that they couldn't continue on their northward course that Papanicolaou realised that they couldn't complete his 'odyssey' and so they decided to return back to the port.

Question: 'He didn't use Medicine to earn money'. We would like to have your comment on this.

Answer: He did not want to earn money from his method, the Pap smear-test. He used to say that in Greece they charge more for the Pap smear-test than in his own Laboratory. He was always very critical of the faults of the Greek health and academic system at that time.

Question: Another interesting point in your work is that you highlighted the supportive role of his life companion, his wife Mache, known as Mary Papanicolaou. How important was the support that he received from her during their first years in the USA as well as during the period before the acceptance of his test?

Answer: His wife Mache-Mary Papanicolaou offered him the main support during the first years in the USA as well as during his research hard years. She was always standing by him, as a 'rock', as a real 'rock'. Despite her short stature, she was always there to listen to him, to tell him her opinion, to support him.

She was his lifelong dedicated companion. She was his whole life. She was always proud of him. And he was always proud of her.

Question: How difficult was the beginning of Exfoliative Cytology, its official recognition and its introduction into clinical practice?

Answer: It was very difficult; gynaecologists, as well as pathologists were always arguing with each other. However, during my time in the USA, Exfoliative Cytology had already been officially recognised and I was the first, who organised the Laboratory of Exfoliative Cytology in the University of Florida. However, the establishment of our Exfoliative Cytology as a specialty still has problems that have to be managed and corrected.

Question: The Pap smear-test is the first 'Virology' test in the history of Medicine with clinical predictive value. We would like to have your opinion on this statement.

Answer: At that time, the scientific field of Virology was not known at all to us. Almost 10 years after the unexpected death of Dr Papanicolaou, - we lost him so unexpectedly (tears appeared in her eyes...) - cervical cancer was proposed to be the result of a viral infection and the cells with the precancerous lesions described by him were cells infected with HPV. Dr Papanicolaou would have been definitely very impressed by Professor Harald zur Hausen's discovery.

Question: 'Καλώς το' (Kalos to). His 'welcome' to you represents his 'welcome' to all the medical students and trainees, who have Dr George Papanicolaou as a model in their career and who are inspired by him. What could be the modern advice of Dr George Papanicolaou to the young medical students and trainees of 2017?

Answer: His welcome with the Greek 'Kalos to' - I don't know if he used it often for his visitors - for me, still sounds in my ears. His welcome was accompanied with a big paternal hug, as

the big hug of the father to his daughter. I think that his advice to the young medical students and trainees would have been the same, as during that time: Hard work, dedication, systematic and continuous studying, and discipline.

Question: We would like to congratulate you for your really touching and valuable, recently published, work entitled 'Dr George and Mache-Mary Papanicolaou - As I knew them' and would like to thank you for your wise answers. We are looking forward to your presence at the 3rd Workshop on Paediatric Virology.

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