Pregledni rad Acta med-hist Adriat 2014; 12(1);181-188
Review article UDK: 616-076.5''20''(091)

50 YEARS AFTER THE DEATH OF GEORGE NICHOLAS PAPANICOLAOU (1883-1962): EVALUATION OF HIS SCIENTIFIC WORK

OCJENA ZNANSTVENOG DJELOVANJA GEORGA NICHOLASA PAPANICOLAOUA 50 GODINA OD NJEGOVE SMRTI (1883.-1962.)

Aristidis Diamantis[1], Emmanouil Magiorkinis[1], Helen Koutselini[2]

Summary

The purpose of this review article is to summarise the scientific work of George Nicholas Papanicolaou, one of the most eminent figures in the 20th century history of clinical cytology and medicine. Fifty years after his death, his work still remains invaluable, from the early steps in biology and zoology to the application of the Pap test as the most important advancement in the prevention of cervical cancer. The publication of his Atlas was the first important step for the foundation of a new branch in medicine, that of exfoliative cytology. His contribution to cytology undoubtedly earned him the title of the "father of exfoliative cytology" and saved the lives of many women worldwide.

***Key words**: History of medicine; 20th century; Papanicolaou; Pap test; exfoliative; cytology*

The work of George Nicholas Papanicolaou has been praised by people of science and culture all over the world. Any attempt to summarise his scientific contributions as a great benefactor of humanity or to assess his enormous scientific work, which literally 'saved the lives of women all over the world',

1 Department of Cytopathology, Naval Hospital of Athens, Greece.
2 Associate Professor of Pathology and Cytopathology, Athens University Medical School, Athens, Greece.
Corresponding Author: E. Magiorkinis BSc, MD, PhD, Georgiou Papandreou, 94. Salamina, Greece. E-mail: emmanouil.magiorkinis@gmail.com

would surely be incomplete. Such an attempt would require a collective effort and profound knowledge of cytology. However, we will try to focus on the hallmarks of his scientific odyssey, which formed the basis of modern cytology.

Fig. 1 - George Nicholas Papanicolaou (1883-1962) in his laboratory

Sl. 1 - George Nicholas Papanicolaou (1883.-1962.) u laboratoriju

Papanicolaou's scientific debut was his 1910 doctoral thesis entitled "Sex differentiation of the daphnia" [1], which was completed at the Zoological Institute of Munich under the supervision of Professor Richard Hertwing (1850–1937). The results of this thesis provided key information for interpreting experiments on sex and heredity that were conducted by the American geneticist and Columbia University professor Thomas Morgan (1866–1945). Morgan mediated for Papanicolaou's appointment to the Department of Pathology and Bacteriology at New York Hospital as an assistant and later to the Department of Anatomy at Cornell Medical School headed by Professor Charles Stockard (1879–1939). During that period, Papanicolaou worked tirelessly to win all the titles in the academic hierarchy.

Papanicolaou's research initially focused on the effects of alcoholic fumes on guinea pigs [2]. He then turned to studying vaginal secretions of guinea pigs, cellular morphology in particular, which varies during the menstrual cycle. He published his research in 1917 in a prestigious journals of his time, Journal of Anatomy, today's equivalent to *Science* or the *American Journal of Anatomy*, setting the course for his later research. He then expanded research on vaginal secretions to women, starting with a case study of his own wife Mary (Mache Mavroyeni, 1890-1982) [3,4]. In 1925, he published his first paper in the *Proceedings of Society of Experimental Biology and Medicine*, presenting the results of his studies in pregnant women [5].

Papanicolaou also pioneered in the research on the hormonal cycle of mammals. He studied the morphology of vaginal and cervical smears in connection with various hormonal changes in females. 'The sexual cycle in

the human female as revealed by vaginal smears' published in the *American Journal of Anatomy* in 1933 as the first study of hormonal cytology promoted using vaginal smears to control hormonal 'status' in women [6]. In this paper, Papanicolaou described cell morphology and the staining method that would later become known as the Papanicolaou test. He also divided the menstrual cycle into four phases (menstruation period: days 1-7; connective phase: days 8-12; exfoliative period: days 13-17; and pre-menstruation period: from day 18 to the new menstruation period).

Professor George Corner (1889–1981), one of the most famous researchers in the field of reproduction endocrinology, claimed that the discovery of ovarian hormones by the American anatomist and physiologist Edgar Allen (1892-1943) and biochemist Edward Doisy (1891–1986), who received the Nobel Prize in 1943, was based on Papanicolaou's method. According to Corner, the association between the knowledge of the menstrual cycle of guinea pigs and the reproductive cycle in rabbits led to the discovery of the luteinizing hormone (LH) and to the complete and profound understanding of the phenomenon in comparison with past theories [7].

During the 1920s, while conducting research on vaginal smears at the Women's Hospital in New York, Papanicolaou noticed cancer cells in women with cervical cancer. This gave him the idea that a systematic study of vaginal smears could lead to early detection of cervical cancer. In January 1928, Papanicolaou announced his results at the Third Race Betterment Conference in Battle Creek, Michigan, USA. The results were published in the conference proceedings under the title 'New cancer diagnosis'. In this paper, Papanicolaou described a new method for the diagnosis of cancer now known as the Pap test. As it usually happens, Papanicolaou failed to convince his peers of the importance of his discovery; instead, he received scathing criticism. Summarising his study, Papanicolaou referred to the advantages of his method: "First: we have a new diagnostic method for certain malignant tumors, especially of the female tract. Second: the methods and the technique used are very simple ones, and can easily be applied in every case. Third: the recognition of malignancy is based not only on the presence of malignant cells but also on the reaction of the organisms itself. Fourth: we have a better understanding of the situation in a cancer case, and we may have some help in analyzing the cancer problem in the future. I think this work will be carried a little further, and analogous methods may be applied in the recognition of cancers in other organs" [8].

Fig. 2 - George Nicholas Papanicolaou on a 10,000 drachma bill from 1995

Sl. 2. George Nicholas Papanicolaou na novčanici od 10.000 drahmi izdanoj 1995.

Eleven years after this first announcement, Papanicolaou shared his beliefs with Professor Joseph Hinsey (1901–1981), who succeeded Stockard in 1939 as the director of the Department of Anatomy at Cornell University, and with Professor Henricus Stander (1894–1948), who was the head of the Department of Gynecology. Both of them encouraged Papanicolaou to focus his research on the development of this new method for the diagnosis of cancer and to cooperate with Herbert Traut (1894–1963), a renowned gynaecologist and pathologist at Cornell University, who specialised in female histological preparations. Their co-operation proved to be extremely fruitful, and the first result of their common research was their well-known paper 'The diagnostic value of vaginal smears in carcinoma of the uterus', which was presented to the New York Gynecological Society in 1941 and published in the prestigious *American Journal of Obstetrics and Gynecology* [9].

In 1943, Traut and Papanicolaou published their monograph entitled 'Diagnosis of uterine cancer by the vaginal smear', which was funded by the Commonwealth Fund [10] and was wonderfully illustrated by drawings of exfoliated cells by a Japanese artist Hashime Murayama (1879-1954). In this 61-page study, Papanicolaou and Traut stressed the importance of the Pap test and described their method in detail. On pages 2-3, they speak of the limitation of vaginal smears, as this technique is not sufficient for definitive diagnosis but should serve as a screening test to be confirmed by histological findings. Moreover, they stress that the assessment of isolated cells or cells in small aggregates requires profound knowledge of cytology, greater than the

one needed to identify abnormal cellular elements in the basal lamina in histological preparations. Papanicolaou was certain that those who would use his technique in the study of vaginal smears would also face the issue of atypical cells, which may point to cancer, but do not suffice for definitive diagnosis. He believed that microscopy of vaginal smears for the detection of immature, neoplasmatic and malignant cells corresponded to the microscopy of haematological preparations for the diagnosis of haematopoietic disorders and that a diagnosis can be safe when multiple cytological preparations have been examined.

Fig. 3. Dr Papanicolaou on a commemorative stamp issued in the US to promote early cancer detection

Sl. 3. Dr. Papanicolaou na prigodnoj marci izdanoj u SAD u promociji ranog otkrivanja raka

In 1948, Papanicolaou and Traut collaborated with Andrew Marchetti (1901–1970), a gynaecologist and later a professor of gynaecology and obstetrics at Georgetown University Hospital, to publish 'The epithelia of woman's reproductive organs', that was later used as a textbook, as it offered important guidance for pathologists and cytologists studying the female reproductive system [11]. One year later, in 1949, Samuel R. M. Reynolds (1903-1982), professor of anatomy, noted that this paper was an important advancement in medicine since it illustrated well the distinction between abnormal vaginal cellular forms from women with genital malignancy. According to Reynolds, this paper provides the most complete set of coloured cell structure images of the female reproductive system than any of the earlier studies. Reynolds stressed that this study was particularly important for the physicians who dealt with the female reproductive organs including those specializing in obstetrics and gynaecology [12].

When Papanicolaou completed the *Atlas of Exfoliative Cytology*, a monumental work funded by the Commonwealth Fund (Harvard Press), he

referred to it in a letter to Marchetti in 1954, as follows: "The Atlas is one of the latest milestones of my contributions to Science. I thank God for allowing me to live long enough and have the energy needed to complete it" [13].

The complete works of Papanicolaou as the "founder" of exfoliative cytology include 158 original articles, all of which are summarised in his monographs. A few years before his death, Papanicolaou was fortunate to receive recognition and honours for his work. The *Atlas of Exfoliative Cytology* was published in two complementary editions in 1956 and 1960. At the International Conference of Applied Exfoliative Cytology, which took place in Brussels on 11-13 July 1957, Papanicolaou addressed the conference as its Honorary President by stressing the importance of this new medical discipline. In his inaugural speech entitled "Historical development of cytology as a tool in clinical medicine and in cancer research" Papanicolaou observed that the most important benefit of exfoliative cytology was that it offered the means to discover cancer at its initial stages. This, according to Papanicolaou, was a major contribution of science to humanity. He also stressed that a big part of our knowledge in cytology and histopathology of early cancer was connected with cervical cancer, since the cervix of uterus is easily accessible for cytological and histological studies. Papanicolaou mentioned that the majority of intra-epithelial lesions (precancerous lesions) and carcinomas *in situ*, which are identified with cytological tests, had provided enough material for cytologists to study cervical cancer pathology and enabled clinicians to treat cancer at an earlier stage [14].

In the years that followed, it became evident how tremendous the impact of Papanicolaou's discovery was on social, medical and economic aspects of life. In fact, the early diagnosis of cervical cancer using the Pap test can serve as a paradigm for the impact of basic research on applied research. It is not always easy to predict the future applications of a finding of basic research in everyday clinical practice; and not even Papanicolaou himself could ever imagine the magnitude of his contribution to the medical community and society. Since the discovery of the Pap test and its introduction in everyday clinical practice, the incidence of cervical cancer in the US alone declined over 60% from 1950 to 1992. If Papanicolaou were alive, he would surely be surprised by the progress that has been made in the field of exfoliative cytology!

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Sažetak

Cilj je članka dati kratak pregled znanstvenog djelovanja Georgea Nicholasa Papanicolaoua, jednog od najznačajnijih ličnosti u povijesti kliničke citologije i medicine XX. stoljeća. Pedeset godina nakon njegove smrti, njegova je ostavština i dalje neprocjenjiva, od prvih koraka u biologiji i zoologiji pa do primjene Papa-testa, kao najznačajnijeg napretka u sprječavanju raka vrata maternice. Izdavanje njegova Atlasa *bio je prvi važan korak u stvaranju nove grane medicine – eksfolijativne citologije. Doprinos koji je dao citologiji osigurao mu je naziv "oca eksfolijativne citologije", a mnogim ženama diljem svijeta spasio je život.*

Ključne riječi: *povijest medicine; XX. stoljeće; Papanicolau; Papa-test; eksfolijativna citologija.*