The Century for Cytopathology

Bernard Naylor, M.B., Ch.B., F.I.A.C., F.R.C.Path.

By the end of the 19th century, exfoliated cancer cells had been described in all of the types of specimen in which we find them today. However, it was not until Drs. Papanicolaou and Traut published their account of the diagnosis of uterine cancer from exfoliated cells (1941 and 1943) that cytopathology acquired the momentum to develop into the powerful presence that it has in human medicine today. These and the subsequent publications by Papanicolaou stimulated the development and application of cytopathology worldwide, resulting in abundant literature on the subject and a galaxy of outstanding practitioners. The 1980s saw the development and widespread use of aspiration cytology. This was followed in the 1990s by the development of automated screening systems, marking the latest stage in the evolution of cytopathology. These and other events and achievements in cytopathology, from its meager beginnings in the early 20th century to its worldwide use and acceptance today, mark this century as the “century for cytopathology.”


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As this century draws to its close, the American Society of Cytopathology invited me to give an account of the main events and achievements in cytopathology in the 20th century, the century when cytopathology developed from meager beginnings to become the powerful presence that it is in human medicine today. In fact, it has been only since 1941 that cytopathology acquired the momentum to develop into a well-established discipline, a discipline that initially most pathologists were not interested in embracing but which now rests securely within the purview of anatomic pathology.

The Early Historical Era

To appreciate fully the achievements in cytopathology in this century, it is necessary to make brief mention of some of the relevant developments of the last century. I shall deal with the 19th century very quickly, simply because there is not very much to deal with that would be of interest to this audience.

One of the earliest examples that I have been able to find of what might be considered cytopathology...
"IF THE CANCER HAVE SOFTENED, THE MICROSCOPICAL CHARACTERS OF THAT PRODUCT MAY BE FOUND SOMETIMES IN THE SPUTA."

W.H. Walshe
London, 1851

Figure 1  A quotation from the book (1851) by Dr. W. H. Walshe.

was published in 1851 (Figure 1). It was a simple statement in a book by a Dr. Walshe, of England, in reference to lung cancer: “If the cancer have softened, the microscopical characters of that product may be found sometimes in the sputa.” \(^1\) Walshe provided no illustrations and did not inform us as to what the “microscopical characters” were. Three years later Professor Lionel Beale, also of England, included a drawing of unstained cancer cells (Figure 2) in the first edition (1854) of his book *The Microscope and Its Application to Clinical Medicine* \(^2\) (Figure 3). These were modest and not very useful beginnings, but they demonstrated that some physicians were aware of the possibility of finding exfoliated cells of lung cancer in sputum.

Sporadically, the literature of the last century did contain other reports of the finding of exfoliated cancer cells in various exudates or secretions. A superb example, again from England, of exfoliated cancer cells sucked from the back of the throat of a patient who had died of cancer of the pharynx (Figure 4) was published in 1861, \(^3\) 22 years before the birth of Papanicolaou. It is obvious to us today that the patient died of keratinizing squamous cell carcinoma.

The findings of cells exfoliated from cervical cancer was rarely reported in the last century, and certainly the authors of the reports had no notion of the potential of their observations. The best example I

Figure 2  Exfoliated cancer cells in sputum illustrated in the book (1854) by Prof. Lionel Beale.

Figure 3  Front cover of the 1854 book by Prof. Beale.

Figure 4  Woodcut illustrating cells of squamous cell carcinoma aspirated from the throat of a man who died of cancer of the pharynx.
could find of cells exfoliated from a cervical carcinoma (Figure 5) is from a remarkable atlas published in 1861 by Lebert of Switzerland. However, such reports were regarded as scientific curiosities of no practical value. Furthermore, the examples I have so far demonstrated were of unstained cells.

By the end of the last century, successful staining of cells and tissues had been accomplished, and biopsy was becoming widely practiced. One notable example of stained exfoliated cancer cells was in a paper published in 1896 by Bahrenberg, of Cleveland, Ohio. His paper introduced the cell block technique for the examination of serous fluids—hence the eponym Bahrenberg method, which now seems to be familiar only to connoisseurs of cytologic history.

Figure 5 Cells of a cervical carcinoma illustrated by Lebert in his atlas of 1861.

Figure 7 Title page of the monograph published in 1943 by Papanicolaou and Traut on the diagnosis of uterine cancer by the vaginal smear.

Figure 6 Front cover of the journal issue with the article published in 1941 by Papanicolaou and Traut on the diagnostic value of vaginal smears in carcinoma of the uterus.

Figure 8 Drawing of cells and a biopsy specimen of cervical squamous cell carcinoma.
By the turn of this century exfoliated cancer cells had been described as occurring in all of the types of specimens in which we are accustomed to finding them today. Yet, despite all these observations of the 19th century, no clear idea had emerged on the morphology of cancer cells, nor was there any concept of applying the cytologic method to the diagnosis of cancer or any other diseases. That was the situation 100 years ago.

For the next four decades cytopathology was becalmed: nothing much was happening either at home or abroad. Yes, there was a handful of interesting and useful published papers on cytopathology during the years from 1900 to 1941, particularly those by Bamforth, Dudgeon and Wrigley of Eng-

Figure 9  Dr. George N. Papanicolaou (1883–1962).

Figure 10  Title page of a map of the island of Evia, where Dr. Papanicolaou was born.

Figure 11  Illustration from the map showing the island of Evia and its closeness to mainland Greece. The site of Kymi is indicated on the east coast of the island.
land on respiratory cytopathology, which can be singled out for their clarity of description and quality of results, and the experience of Coley, Ellis, Martin and Stewart with aspiration cytology of a variety of organs from patients in Memorial Hospital for Cancer and Allied Diseases in New York. But beyond these events, nothing remained especially memorable or influential in the field of cytopathology.

The Era of Development and Expansion

This era of cytopathology, which I refer to as the “early historical era,” gave way abruptly to the era of development and expansion in 1941 with the publication by Drs. George Papanicolaou and Herbert Traut, of Cornell University, of their seminal paper in the American Journal of Obstetrics and Gyne-
cology, “The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus”6 (Figure 6), which was followed in 1943 by their famous monograph *Diagnosis of Uterine Cancer by the Vaginal Smear*7 (Figure 7), with its magnificent drawings by Hashime Muryama of exfoliated cells and tissues (Figure 8).

Gynecologists immediately grasped the significance of these publications. However, many pathologists remained very skeptical about the ability to diagnose cancer by examining dropped-off cells. After all, the all-important hallmark of cancer was invasion of tissue, a feature not perceptible in cytologic preparations.

**Dr. George N. Papanicolaou**

Since the name *Papanicolaou* is so frequently uttered in cytologic practice, you may ask who was this man (Figure 9) whose name, albeit in an abbreviated form, provides the medical eponym that is probably the most widely used throughout the world today?

One of the largest of the Greek Aegean islands is Evia (Figure 10), situated so close to the Greek mainland (Figure 11) that the two are connected by a causeway. On the east coast of Evia lies the small town of Kymi, where Papanicolaou was born. If, on Sunday, May 15, 1983, you had entered Kymi, signs of celebration (Figure 12) would have welcomed you, for the town was commemorating the 100th anniversary of the birth of its famous son. Naturally, speeches were made, with representatives of the church, military and government in attendance (Figure 13). If you had then walked down a certain narrow street near the center of the town, you would have passed by his house (Figure 14) with its typical Mediterranean facade. Passing by at the right moment (Figure 15), you would have found a crowd gathered outside the house; on approaching the crowd, you would have witnessed (Figure 16) the mayor of Kymi unveiling a plaque inscribed (in translation), *The House Where G. Papanicolaou Was Born* (Figure 17). Not only was he born in this house in 1883, he spent his early childhood there. Once inside the house, it was easy to see that it was a substantial building, in keeping with the position his father held as a general practitioner and one-time mayor of Kymi.

George Papanicolaou graduated in medicine from the University of Athens in 1904 and decided early in his professional life that, unlike his father, general practice was not for him. He subsequently...
NEW CANCER DIAGNOSIS

Dr. George N. Papanicolaou
Cornell University Medical College

Figure 18 Title page of the paper delivered by Dr. Papanicolaou in Battle Creek, Michigan, in January 1928.

worked as a physiologist on the oceanographic vessel L’Hirondelle II of Prince Albert I of Monaco, acquired a doctorate in philosophy in natural sciences from the University of Munich and served in the Greek army during the Balkan wars. While serving in the army he associated with Americans, volunteers to the Greek cause, and listened to tales of their country.

Obviously, he liked what he heard about the New World, for in 1913 Dr. and Mrs. Papanicolaou emigrated to the United States, where he obtained a position in the Department of Anatomy at Cornell University in New York City. There he began research on the estrous cycle of mammals, using cellular samples from the vagina of guinea pigs. He extended this work to humans, for which he obtained specimens from various gynecology clinics in New York City. Inevitably, he received vaginal smears from women with cervical cancer, and the cancer cells they contained he recognized as such. He was not searching for cancer cells; he observed and recognized them serendipitously.

As I have mentioned already, the presence of cancer cells in vaginal smears had been briefly illustrated in publications of the last century. What made Papanicolaou’s work different was that he realized the importance of wet fixation of cytologic specimens, he developed a fine stain for exfoliated cells, and he systematically began to accumulate examples of cancer cells in vaginal smears from humans, which culminated in a paper titled “New Cancer Diagnosis”8 (Figure 18), which he presented at the Third Race Betterment Conference in Battle Creek, Michigan, in January 1928 (Figure 19), in the Battle Creek Sanitorium (Figure 20), now the Battle Creek Federal Center (Figure 21). (Battle Creek, in southern Michigan, is not well known because of Dr. Papanicolaou’s presentation there. It is well known, at least in the United States, because it is the world headquarters of Kellogg, the cereal maker).

Figure 20 Battle Creek Sanitorium, Battle Creek, Michigan, where Dr. Papanicolaou gave his paper in 1928.

Figure 21 Main entrance of the sanitorium, now the Battle Creek Federal Center.
By a curious coincidence, a distinguished academic pathologist in Rumania, Dr. Aurel Babeş (Figure 22), also published an article on the subject at virtually the same time Papanicolaou gave his presentation in Battle Creek in January 1928. Babeş' article, “Diagnostic du cancer du col utérin par les frottis” (“The Diagnosis of Cancer of the Uterine Cervix from Smears”), appeared in *La Presse Médicale* in April 1928 (Figure 23). It had been preceded by the presentation of his findings (Figure 24) at two sessions of the Bucharest Society of Gynecology in 1927. However, Babeş' technique of preparing, staining and examining vaginal smears was very different from Papanicolaou's and, without modification, certainly would not have lent itself to mass screening.

Figure 24  Title page of a paper by Professor M. Daniel and Dr. A. Babeş on the diagnosis of cervical cancer from smears, presented to the Bucharest Society of Gynecology on April 5, 1927.

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Figure 25  Papanicolaou Cancer Research Institute in Miami. Dr. Papanicolaou became its director in November 1961.
The reason that the name Babeş, whose lifespan (1886–1961) was almost the same as that of Papanicolaou (1883–1962), is not generally associated with cytopathology is that apart from one additional brief reference to cervical cytology in 1931, he did not publish another paper on cytopathology, in contrast to Papanicolaou, who published scores. Did Papanicolaou and Babeş hear of each other’s work? Circumstantial evidence, including an article by the widow of Babeş\(^\text{11}\) leaves no doubt in my mind that Babeş was acquainted with the writings of Papanicolaou; however, Papanicolaou, in his numerous writings, never gave any hint of familiarity with Babeş articles of 1928 and 1931.

On the morning of Friday, February 16, 1962, I tracked down Babeş article of 1928 in the medical library of the University of Miami and brought it to the institute in Miami where Dr. Papanicolaou had recently taken up the directorship. I briefly told him what I had found and suggested that I show it to him on Monday because he was just about to meet an important visitor who would be his house guest over the weekend. During our very brief exchange, Dr. Papanicolaou gave no intimation of being aware of the existence of Babeş article. By the Monday morning, three days later, when I would have shown him the article, Dr. Papanicolaou had died of a heart attack.

To complete this sketch of Papanicolaou’s professional life after his retirement from Cornell University in 1951, he remained there carrying out re-

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**Figure 26** Group outside the Papanicolaou Cancer Research Institute in Miami about two weeks before Dr. Papanicolaou died. Front row, from left to right: Drs. Papanicolaou, Philip Archer, Bernard Naylor, Irena Koprowska and John R. McDonald.

**Figure 27** Dr. Ruth M. Graham (1917–1978). Courtesy of Susan M. Graham.

**Figure 28** *The Cytologic Diagnosis of Cancer*, by Dr. Ruth M. Graham and her staff at Vincent Memorial Hospital, Boston. This book, published in 1950, was a most important landmark in the history of cytopathology.
As mentioned previously, the publications of Papanicolaou and Traut in 1941 and 1943 began the second era of cytopathology, the era of development and expansion. This era saw the advent of cytologic screening for cervical cancer, which revealed not only that a large pool of undetected cervical cancer existed in North America and elsewhere but that its detection by cytologic screening was possible and practical. With this development, the cytologic method of cancer diagnosis began to be more widely applied to the respiratory, alimentary and urinary tracts as well as to the serous cavities and the central nervous system.

By 1945 Dr. Joe V. Meigs, doyen of American gynecologists, and his colleagues at Massachusetts Hospital had confirmed the soundness of the cytologic method in the diagnosis of cervical cancer, including its in situ phase. In this endeavor, Dr. Meigs was assisted by a zoology graduate who had subsequently trained as a medical technologist, Ruth Graham (Figure 27). She established the cytopathol-
ogy laboratory at Massachusetts General Hospital and, with her team of cytotechnologists, produced one of the most outstanding books (Figure 28) on the morphology of exfoliated cancer cells ever written, *The Cytologic Diagnosis of Cancer.*\(^\text{12}\) Ruth Graham receded prematurely from the cytology scene and died in 1978. Consequently, her book, which had been widely used in the training of cytotechnologists and cytopathologists (including myself), has fallen into disuse.

Pathologists soon realized that no matter how much cytologic expertise they possessed, they could not put it to use unless they were supported by trained cytotechnologists. In the 1950s, formal training programs for cytotechnologists began to develop, and by 1976 more than 100 programs were in existence. The training of cytotechnologists in North America has been an outstanding success story.

As for the serious training of pathologists in cytopathology, it lagged behind except in those few residency programs where there were seasoned and enthusiastic cytopathologists who were able and willing to impart their diagnostic skills to their residents. Now the situation has greatly improved. The American Board of Pathology now includes a significant cytopathology component in its basic certifying examination and in 1988 introduced a certificate of special competence in cytopathology, a tremendous stimulus to acquiring competence in cytopathology.

*The Era of Consolidation*

A third era of cytopathology, the era of consolidation, was heralded by the appearance of two publi-
cations: the first issue of *Acta Cytologica* (Figure 29) in 1957, under the editorship of Dr. George Wied, and four years later, in 1961, publication of *Diagnostic Cytology and Its Histopathologic Bases* (Figure 30) by Dr. Leopold Koss.

For 42 years, *Acta Cytologica* has been the international forum dedicated to the exchange of ideas and the publication of research in cytopathology. For the continuity of this journal and the standards attained in it, we are grateful to its editor-in-chief, Dr. Wied (Figure 31). Not only has Dr. Wied provided the thread of continuity for the journal, but he has also used his great organizational talent to develop educational programs in cytopathology worldwide. The publication by Dr. Koss (Figure 32) of his book in 1961 and its subsequent editions has brought together under one cover not only a body of theoretical and practical knowledge of cytopathology but also the correlation between cytopathology and histopathology, a matter of outstanding importance to anatomic pathologists who practice cytopathology. This book has been a momentous achievement.

In the time allocated for me to address you today, it is clearly impossible to even attempt to mention all of those other persons who have made significant and lasting contributions to cytopathology; I see several of them in the audience. I would be remiss, however, if I were not to mention a few of the other leading protagonists of the 20th century’s cytopathologic drama.

Some of you may recall that the literature of the 1950s through the 1970s contained a steady stream of articles by the late Drs. James Reagan (Figure 33) and Stanley Patten (Figure 34) at Case Western Reserve University. The work of Drs. Reagan and Patten was most notable in that it applied the laborious techniques of planimetry and objective cell measurement to the analysis of cellular samples from the female genital tract in order to establish reliable and reproducible diagnostic criteria. Their foresight...
heralded today’s explosive growth of research into the clinical application of quantitative morphometric analysis of cells and tissues in many areas of anatomic pathology.

One of the earliest and strongest advocates of cytopathology, especially cervical cytology, was Dr. J. Ernest Ayre (Figure 35), a gynecologist turned cytopathologist. He was the person who, in 1948, introduced the wooden cervical scraper, the Ayre spatula13 (Figure 36). Almost 50 years ago, Dr. Ayre described the typical histologic changes (Figure 37) brought about in cervical squamous epithelium by infection with human papillomavirus (HPV), a change which he termed the “precancer complex.”14 The cells derived from the lesion (Figure 38) that he illustrated would be readily recognized today as the indisputable manifestation of infection with HPV. However, Dr. Ayre did not realize this, and the nature of the cell remained a mystery.

In 1956, Dr. Koss coined the descriptive term koliocytotic atypia15 for this type of cell (Figure 39), but again its nature remained something of a mystery. Back again to Dr. Ayre; in 1960 he suggested that the changes of koliocytotic atypia were caused by a virus,16 and in 1976 Drs. Alexander Meisels (Figure 40) and Roger Fortin in Québec City published their epochal article, “Condylomatous Lesions of the Cervix and Vagina: I. Cytologic Pattern,”17 which identified the causative agent of this change as HPV.

These observations by Drs. Ayre, Koss and Meisels are probably the most important in the field of gynecologic cytopathology since the introduction of cytology as a diagnostic tool. They opened up a large field of research into the morphogenesis and cause of cervical squamous cell carcinoma. The remarkable story of the koilocyte was recounted by Dr. Meisels in the George N. Papanicolaou Award lecture of 1983, titled “The Story of a Cell” (Figure 41), which was subsequently published in *Acta Cytologica*.18
While nongynecologic cytology sailed along smoothly over the decades to culminate in the development of aspiration cytology, gynecologic cytology in the United States and elsewhere has been the victim of its own success. Because of its ability to detect subclinical cervical carcinoma, its failure to do so in individual cases has resulted in litigation or the threat of litigation, which has profoundly influenced the practice of gynecologic cytopathology.

On November 2, 1987, an exposé appeared in *The Wall Street Journal* describing the excessive demands made of cytotechnologists by certain for-profit, commercial laboratories. This article raised a huge outcry in the news media, which has resulted in stringent federal rules regulating the practice of gynecologic cytopathology but which, after 13 years, has not yet gotten off the ground.

With the prospect of federally mandated proficiency testing, in December 1988 a workshop was convened at the National Cancer Institute, in Bethesda, Maryland, to develop terminology for reporting that would reflect the development of cervical cancer and the near impossibility of discriminating with any degree of consistency between various degrees of squamous intraepithelial neoplasia in cytologic preparations. The outcome of this workshop, The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses, came into being and has largely replaced the outdated reporting system devised by Papanicolaou in the 1940s.

For those of us interested in the historical developments in cytopathology of the 20th century, it is worth noting how the content of *Acta Cytologica* has changed from its earliest issues to the present. It was not until its third volume, in 1959, that *Acta* published an article on nongynecologic cytology. The earliest issues reflected an extreme preoccupation with the application of cytology to the female genital tract. These issues were devoted to such
subjects as the classification of normal cells, the fixation of cervical smears, the cytology of pregnancy, how to report cervical smears and so on. Look at the difference in content today: of the 15 articles published in the latest issue of *Acta Cytologica*, only 4 (27%) dealt exclusively with cervical cytology. Seven (47%) were devoted to some aspect of aspiration cytology, a remarkable development considering that it was not until the eighth year of its existence that *Acta Cytologica* published an article on the subject.

This development of aspiration cytology in the United States in the last two decades came about largely under the influence of the Swedish school of cytopathologists, especially Drs. Sixten Franzén, Joseph Zajicek and Torsten Löwhagen†. Dr. Löwhagen (Figure 43) has received students from many countries, and his contribution to aspiration cytology was formally recognized in 1995 by the American Society of Cytopathology, which conferred on him the George N. Papanicolaou Award.

The widespread development of aspiration cytology was exposed in *The Wall Street Journal*, November 2, 1987, by Walt Bogdanich, exposing “lax” cytopathology laboratories.

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†Dr. Torsten Löwhagen died on December 7, 1999.
ogy is in keeping with a most accurate prediction made to me in a conversation with Dr. Koss in 1978, that one of the biggest advances in anatomic pathology would be the development and application of aspiration cytology. Now there is scarcely a tissue in the human body that has not faced the sharp end of an aspiration needle. The development in aspiration cytology over the last two decades brings us, I believe, to the end of the third era of cytopathology, the era of consolidation.

What will the next era of cytopathology be about? Surely it is about the development and application of automated screening systems for cytopathology, especially gynecologic cytology. The initiative has been grasped by several companies in North America that have developed systems for the primary and secondary screening of cervical smears, with various degrees of success. However, because of cost and other considerations, nearly all cervical smears in North America are still screened manually. It seems to me that the application of automated screening to gynecologic cytology is a high priority, one that will relieve cytotechnologists of the need to spend many hours at the microscope engaged in a repetitious yet demanding task.

In other parts of the world, particularly western Europe, automated screening of cervical smears has been widely adopted, especially under the influence of the much-published and enterprising Dr. Mathilde Boon, of the Netherlands, shown with her physicist husband, Lambrecht Kok (Figure 44), an invaluable collaborator. I am proud to be able to tell
you that Dr. Boon acquired her taste for cytopathology during a sojourn at the University of Michigan.

**Epilogue**

Dr. Papanicolaou is buried in the country of his adoption (Figure 45), not too far from Cornell University Hospital, the scene of most of his cytologic triumphs (Figure 46). Were he alive today, he would be amazed and gratified by the events and the achievements that have taken place in cytopathology since he published his first paper on the subject in 1928: the application of cytology to the diagnosis of cancer in all of the systems of the body, the development of successful screening programs for cervical cancer, the flourishing of aspiration cytology, the application of electron microscopy and immunocytochemistry to cytologic specimens, the development of education and training in cytopathology for cytotechnologists and pathologists, the publication of journals exclusively for cytopathology, the development of numerous societies of cytology and the surge of interest in automated screening systems.

These constitute an impressive list of achievements in this century since Dr. Papanicolaou made the tedious journey by train from New York to Battle Creek almost 72 years ago, a journey that set into motion the events and achievements that surely have earned this century the right to be called the “century for cytopathology (Figure 47).”

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