Criticism of the Pap Smear as a Diagnostic Tool in Cervical Cancer Screening

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Abstract

This editorial by Dr. Leopold G. Koss appeared in the January 1980 issue of *Acta Cytologica*. It addressed recent critical opinions in the general media on cervical screening and its costs. It marked the beginning of a more critical approach to cytology by the lay press, health care providers, and epidemiologists. It was also the first of a series of highly informative editorials by Dr. Koss that illustrated the critical issues of cytology during the 1980s. The elegance and clarity of his articles reflect the high standard of editorial writing in *Acta Cytologica* at this time. These articles are reviewed and excerpts are presented.

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The article by Dr. Leopold G. Koss [1] appeared in the 1980 January/February issue of *Acta Cytologica*, just at the start of the new decade. It was the first of what would become a remarkable series of editorials submitted by this unusually gifted and prolific writer over the next 10 years [1–10]. With outstanding foresight and wit, he addressed an entire spectrum of issues which excited, intrigued, or

Dr. Leopold G. Koss (1920–2012)

even worried the cytologic community. While recently reading through these editorials, I was enchanted by the elegance and clarity of the writing, but even more so by his foresight and the analytical power of his observations. Not surprisingly, many of the questions he raised and discussed are still with us today.

The article “The Attack on the Annual “Pap Smear” [1] was initiated by increasingly critical reports in the lay press on the effectiveness and cost-benefit ratio of cervical screening, exemplified by a cover story in *Newsweek*, entitled “Flap with Pap”. Some of the questions discussed by Dr. Koss are still with us today. Can the cost be reduced by spacing the screening procedure? How well is the

smear being handled in the laboratory? What about the fatigue of the cytotechnologist? What is the risk of progression in the individual patient? However, he also clearly stated that “a large percentage of precancerous lesions detected by cytology will not progress to invasive cancer during the lifetime of the bearer.”

Two editorials [2, 6] on fine-needle aspiration (FNA) appeared in 1980 and 1984, respectively, and illustrated the remarkable take-off of this technique in the USA within these four years. In 1980, Koss outlined the historic development of aspiration cytology and pathology in Europe, particularly in Sweden, and contrasted it with the lack of interest in FNA in the USA, where surgical pathology was still dominant. In 1984, however, the editorial written together with Dr. Wied introduced the first issue of *Acta Cytologica* to be dedicated exclusively to FNA, thereby highlighting the foresight and progressive nature of this journal. The subsequent phenomenal success of this technique worldwide was considerably enhanced and supported by the editorial policy of the journal.

The editorial on environmental carcinogenesis and cytology [3] exemplifies the elegant and all-encompassing style of Koss' writing. Starting with the well-known history of lung cancer in cobalt and radium mine workers in Saxony and Czechoslovakia (in Schneeberg and Joachimsthal, respectively), he then moves on to bladder cancer in industrial workers and its detection by means of urinary cytology. Although several studies on developing lung cancer in uranium workers in Utah and asbestos workers in Texas led to the recognition of squamous metaplasia and dysplasia as precursor lesions of lung cancer, Koss did not see any evidence that screening industrial workers would contribute significantly to improving their survival.

The introduction to his article on cytochemistry in 1984 was classic of Koss' historic and cosmopolitan approach, and should not be missed [7]:

Many a visitor to Paris is familiar with a street on the Left Bank of the Seine known as Boulevard Raspail. The street is named after Francois-Vincent Raspail (1794–1878), a renowned political reformer. It is less well known that this extraordinarily versatile man, who is recognized today as the initiator of microscopic chemistry, started his career as a chemist and microscopist. In 1830, Raspail published a pamphlet, in which he described the application of principles of contemporary chemistry to microscopy. Raspail's work was the beginning of a chain of scientific events lasting to this day that have for their purpose the identification of the precise chemical makeup of cells and tissues.

From there, Koss moves to the history of the dyes still used today in microscopy such as hematoxylin, eosin, and

the Feulgen stain for DNA quantification. He concludes with the development of monoclonal antibodies by Köhler and Milstein [11]; this was hot news in those days whereas today it is daily practice around the world.

Readers who are interested in the development of automation in cytology will thoroughly enjoy the comprehensive editorial entitled “Analytical and Quantitative Cytology: A Historical Perspective” [5]. After detailing the rudimentary beginnings of microscopy, cytochemistry, and cell measurements, Koss gives a personal account of the origins of automation and the people involved, all of whom he knew and worked with personally. The pace of progress, from the beginnings of the “cytoanalyzer” in the 1950s, to the introduction of computers and high-resolution image analysis in the 1970s, and then to flow cytometry, appeared to be painfully slow. However, in 1982, Koss concluded this editorial correctly: “One can imagine that within a foreseeable time, any diagnostic analysis of tissues and cells will be computer generated.... in this proposed scheme of things to come, analytical and quantitative cytology will play a key role.” And indeed, with computer-aided screening in today's laboratories now a routine procedure, his vision was proved correct.

In 1987, a lead article in *The Wall Street Journal* about lax laboratory practices in so-called “Pap-mills” caused havoc in the cytology community and among health authorities. Shortly thereafter, Koss analyzed the situation in an extensive review entitled “The Papanicolaou Test for Cervical Cancer Detection: A Triumph and a Tragedy” [9] published in *JAMA*, the main journal of the American Medical Association. It was an attempt to explain, to lay people and health policy makers alike, the complexity of the cervical cancer detection system. It was a widely quoted article, in which Koss addressed the issues of quality control, the natural history of the lesions, remedies, and sources of errors.

As a consequence, health authorities introduced the “Clinical Laboratory Improvement Act of 1988” with considerably stringent laboratory regulations. In 1989, the cytology community developed The Bethesda System for cytology reporting, which was commented on by Koss in an editorial [10] published in the *Journal of the National Cancer Institute*.

Finally, it is noteworthy and more than appropriate that Koss was the author of a congratulatory editorial on the 25th birthday of *Acta Cytologica* in 1981 [4]. In it, he fondly recalled the arrival of the first issue in 1957, which was in offset printing on thick paper. Under the guidance of the long-term editor, Dr. George L. Wied, he reviewed the successful development of the journal after its difficult

start. He then pondered on the natural course of a scientific journal, and *Acta Cytologica* in particular. The explicit question: “What about the future of *Acta Cytologica*?” is related, for him, to the future of cytology. And this, he saw as bright [4]:

As the emphasis shifts, as it must, to preventive care...the cell sample obtained by a variety of means will increasingly replace the tissue sample as the first diagnostic approach to disease identification...Within the framework of these future changes, the survival of *Acta Cytologica* seems reasonably assured. Dr. Wied and the editorial staff deserve our thanks for the past accomplishments and best wishes for the future.

In summary, the article reprinted here and the series of editorials by Koss in the 1980s give a lively and detailed view on the scientific situation of cytology in the years when *Acta Cytologica* was the only cytologic journal around. In 1990, in honor of Dr. Koss on his 70th birthday, these editorials were reprinted in a special issue, to be reviewed in their entirety [12]. The special issue illustrates an intense period in the field of cytopathology, with its time-specific expectations, hopes, crises, and solutions. It should give us the necessary support and energy

to continue to develop *Acta Cytologica* to new heights in the future.

Dr. Leopold G. Koss (1920–2012) was a member of the Editorial Board of *Acta Cytologica* for more than 50 years and contributed significantly to its success. He was the author of numerous articles published in the journal and a reviewer for many years. He also wrote the most recognized textbook on cytopathology, *Diagnostic Cytology and Its Histopathologic Bases*, which appeared in two volumes and six editions. He was widely traveled and delivered many lectures. George L. Wied, on the occasion of Dr. Koss’ 70th birthday [12]:

Above all, he is one of the few renaissance men in our field. He is versed in art, music, history and languages. His lectures are not only scholarly but also a pleasure for the listener. He is a superb cytopathologist and a good friend, and we wish him many happy returns and many more prolific years.

Disclosure Statement

The author has no conflicts of interest to declare.

Editorial

The Attack on the Annual 'Pap Smear'

Leopold G. Koss, M.D., F.I.A.C.

Annual cytologic screening for cancer of the uterine cervix has become deeply ingrained in American society over the past quarter century. The concept of the annual "Pap smear" presumably originated with the American Cancer Society, which has been actively involved in the advocacy of this test. National Center for Health Statistics data, cited by Marx,⁹ indicate that approximately 56 million Pap smears were performed in the United States in 1974 at an approximate cost of \$200 million to \$250 million. Now this procedure is under attack.

In 1978 Foltz and Kelsey⁴ published a major paper critically reviewing the origin, implementation and value of the annual Pap test. This paper warrants careful reading because it addresses some of the important public health issues connected with the annual administration of a popular cancer prevention procedure. The issues raised concern the cost of the procedure to society and its effectiveness, or the cost-benefit ratio. Is the annual expenditure of a quarter of a billion dollars worthwhile? Does the Pap smear save lives? Who should be screened, and how? What is known about the reliability of the procedure as a cancer detection device?

The Foltz and Kelsey message did not go unnoticed. A few months ago, *Newsweek*, the popular weekly publication with a wide readership, spoke of "Flap with Pap." More important, however, the

theme was recently reviewed by the prestigious *Science* under the title "The Annual Pap Smear: An Idea Whose Time Has Gone?"⁹ The writer, Jean L. Marx, concluded her remarks with a gingerly endorsement of the test per se but shared some of the misgivings expressed by Foltz and Kelsey. She complained of the lack of guidance on the part of the National Cancer Institute in this matter and cited extensively from the Walton report,¹³ which proposed a number of policies for screening women for cervical cancer in Canada.

It is obvious that the issues concerning the cervical smear are of particular interest to the readers of *Acta Cytologica* and to members of the many affiliated national societies of cytology. It is equally obvious that the matter of the effectiveness of the Pap smear and its cost-benefit ratio must be carefully considered. I have repeatedly discussed some of these problems in public forums without much response. Because a large volume of cervical smears is now in the hands of profit-oriented laboratory organizations, there is much vested interest in the continuation of the status quo.

Unfortunately, the answers to some of the questions raised by the lay writers (Foltz, Kelsey and Marx are not physicians) are extremely complex. Is the Pap smear cost effective? The answer clearly depends on the definition of cost effectiveness and the economic factors governing this definition. Even the Walton report, perhaps the most scholarly discussion of cervical cancer screening programs to date, avoids this issue and states that the "economic aspects of screening for cancer of the cervix would be out of place in this report." The overall huge cost of the annual Pap smear to American society is dispersed because the procedure is not covered by a central insurance system. There is no information available on the actual cost of some of the most successful programs, such as those conducted in British Columbia,³ Jefferson County, Kentucky,¹ and Iceland,⁷ all of which have demonstrated that cytologic screening reduces the rate of invasive cancer of the cervix. The gift of life to a woman is obviously priceless. The Foltz and Kelsey question "How much does it really cost and can the Society afford it?" cannot be answered authoritatively without supporting fiscal data and the consideration of the ethical and moral factors which enter into the equation.

Can the cost be reduced by spacing the screening procedure, at least for women not at risk, as suggested by the Walton report? It seems reasonable to assume that the socially stable woman with limited

sexual exposure who had three prior negative smears is at an extremely low risk of developing cervical cancer and could be safely screened every second or third year. It seems equally reasonable to assume that a socially unstable, promiscuous woman should continue to have annual screenings. When I made this suggestion at a recent talk in Ohio, a member of the audience objected, stating that in his community "there were no low-risk women." Obviously, the annual Pap smear is the one procedure in cancer prevention that has gained a high level of social and professional acceptance. The annual procedure offers some additional intangible benefits, such as the annual attention to health matters in general. Are the risks of obliterating this accepted discipline by a less structured approach worthy of the fiscal savings? At this time there is no information on the results of the Walton recommendations, and none can be expected for several years. The initial results of the Swedish experience, limited for fiscal reasons to smears obtained every four years, cast some doubt on the wisdom of this approach.¹¹

Is the consumer, i.e., the screened woman, receiving good value for her money? In other words, is she buying a product (in this case a cytologic diagnosis) that is of top quality and reliability? Does the smear, as submitted to the laboratory, faithfully reflect the status of the epithelium? There are no fully reliable objective criteria to identify an "adequate" smear. The presence or absence of endocervical cells is, in my judgment, a poor criterion of adequacy because it depends not only on the method used to obtain the smear but also on the age of the patient and other clinical circumstances. The use of ancillary procedures, such as the endocervical aspiration, has not gained broad acceptance among clinicians, and its overall contribution to the diagnosis of precancerous lesions of the cervix must be considered modest.

Regardless of these considerations, how reliable is the Pap smear? A consensus has been developing that a single smear carries with it an unspecified, but significant, margin of error.² It has been shown that two simultaneous smears are better than one.¹² Are three smears better than two? What is the cost effectiveness of multiple smears? What is gained and what is lost by this approach? A truly controlled, scientific study of the effectiveness of the cervical smear, using optimal cytologic and colposcopic techniques and a long-term follow-up of a large population of women, has never been done. It would be an extremely costly study and perhaps could no longer be conducted in the United States, where a previously unscreened

population of women would be difficult to identify. Perhaps some form of partnership could be developed with another country where, in exchange for the benefits of screening, a long-term study of this type could be initiated.

Assuming the optimal quality of the smear, how well is it handled by the laboratory? Anecdotal knowledge suggests that significant differences in performance and reliability exist among laboratories. What about factors such as human fatigue? What is really known about the cytotechnologist's ability to perceive minor cell abnormalities after one, two, six or eight hours of screening? What tests do we apply to determine whether the persons to whom we entrust the screening and diagnostic tasks have the talent, ability and stamina to identify cell changes? There is obviously much that still awaits some fundamental inquiries.

A further matter that is raised by Foltz and Kelsey is the nature of the intraepithelial changes detected by smears and the natural history of the disease. There is little doubt that a large percentage of precancerous lesions detected by cytology will not progress to invasive cancer during the lifetime of the bearer. The question of morphologic identification of the lesions with good prognosis versus the lesions with bad prognosis still eludes us. Personal experience suggests that morphology alone does not provide the answers. Are there any other helpful criteria? The evidence available at this time, based on sophisticated studies of DNA distribution, gives us confusing answers. One study, based on evaluation of the DNA content of cells in smears, strongly suggested the inability of the human observer to identify the future behavior of the precancerous lesions.¹⁰ A similar study, based on tissue samples, reached the opposite conclusion.⁵

Population studies have repeatedly shown that the rate of invasive cancer of the uterine cervix drops in the competently screened populations.^{1,3,7} Yet, in some countries the effect of screening apparently cannot be translated into a clear social and health benefit.⁶ In Sweden, evidence has been presented that invasive cancer of the cervix may occur in previously screened populations as a consequence of inadequate laboratory and clinical handling of patients.¹¹ Available data suggest that this experience is not confined to Sweden and has also been observed in the United States⁸—obviously a matter of great concern.

These and related matters not specifically mentioned in this brief overview are obviously worthy of further study. Regardless of some opinions to the contrary,⁶ none of the questions raised have seriously undermined the basic premise of cervical cytology, namely, that well-run programs of cytology screening for precursor lesions are effective in reducing mortality from invasive carcinoma of the uterine cervix. However, in the climate of consumer inquiry in which we live, it may prove worthwhile to review critically the accepted customs and to try to provide some answers to the questions raised.

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