A Note from History:  
The Link between Koilocytes and Human Papillomaviruses

Steven I. Hajdu

Keywords: history of clinical science, history of cytology, human papillomaviruses, koilocytes

Condylomas (condylomata acuminata) and genital warts (verrucous papillomas) have been recognized as human diseases since ancient times [1]. The first microscopic illustration of the squamous cells of a verrucous lesion was published in 1845 [2].

In 1941, an innovative smear technique for vaginal cytology (later known as the “Pap Smear”) was introduced in New York City [3]. Within a few years, numerous cytologic observations were made on smear preparations by a new breed of physicians, ie, cytologists. In 1951, a Canadian gynecologist-cytologist, J. Ernest Ayre, while working in Miami, Florida, first described and illustrated squamous epithelial cells with a perinuclear “halo” in smears of the uterine cervix [4]. He described the “halo cells” with perinuclear “clearing” as mononucleated or binucleated poorly keratinized squamous cells with hyperchromatic (atypical) nuclei. Ayre advanced the notion that the squamous cells with perinuclear halo or “vacuole” were “pre-cancer” cells and were always found in association with chronic inflammatory cells (Fig. 1). He believed that long-standing inflammation or infection (viral or some other kind) was involved in the occurrence of these odd looking squamous cells and that the perinuclear vacuoles represented degenerative changes [4].

Ayre’s observation attracted the attention of others and in 1956 Koss and Durfee [5], at the Memorial Sloan Kettering Cancer Center in New York City, named the squamous cells with enlarged nuclei and sharply demarcated perinuclear clear zone, surrounded by a rim of cytoplasm, “koilocytes” (from Greek, a hollow cell) [5]. The term koilocyte was promptly accepted as a descriptive name for the squamous cells with peculiar nuclear and cytoplasmic changes of unknown origin and uncertain significance.

Although cytologists were occupied diagnosing koilocytes, atypical cells, and cancer cells, the cause of condylomas, squamous papillomas, and the source of the koilocytic changes remained obscure for two decades. It was almost forgotten that in the

Condylomas (condylomata acuminata) and genital warts (verrucous papillomas) have been recognized as human diseases since ancient times [1]. The first microscopic illustration of the squamous cells of a verrucous lesion was published in 1845 [2].

In 1941, an innovative smear technique for vaginal cytology (later known as the “Pap Smear”) was introduced in New York City [3]. Within a few years, numerous cytologic observations were made on smear preparations by a new breed of physicians, ie, cytologists. In 1951, a Canadian gynecologist-cytologist, J. Ernest Ayre, while working in Miami, Florida, first described and illustrated squamous epithelial cells with a perinuclear “halo” in smears of the uterine cervix [4]. He described the “halo cells” with perinuclear “clearing” as mononucleated or binucleated poorly keratinized squamous cells with hyperchromatic (atypical) nuclei. Ayre advanced the notion that the squamous cells with perinuclear halo or “vacuole” were “pre-cancer” cells and were always found in association with chronic inflammatory cells (Fig. 1). He believed that long-standing inflammation or infection (viral or some other kind) was involved in the occurrence of these odd looking squamous cells and that the perinuclear vacuoles represented degenerative changes [4].

Ayre’s observation attracted the attention of others and in 1956 Koss and Durfee [5], at the Memorial Sloan Kettering Cancer Center in New York City, named the squamous cells with enlarged nuclei and sharply demarcated perinuclear clear

Address correspondence to Steven I. Hajdu, M.D., 1759 Drumcliff Court, Westlake Village, CA 91361, USA; tel 805-496-0691; fax 805-496-0620

Fig. 1. Atypical squamous cells (see arrows labelled 1, 2, and 4) with hyperchromatic nuclei and perinuclear vacuoles, which are so-called “halo” cells (later named koilocytes) in a cervical smear [1].
early 1930s squamous papillomas in rabbits had been linked to a transmissible viral agent and that the papillomas were capable of progressing to cancer [6].

The veil of obscurity began to be lifted in 1968 by the electron microscopic finding of viral particles in genital condylomata acuminata [7]. The “wart virus” having been identified, a search began to link koilocytes and other squamous atypias to viral infection. The years 1976 and 1977 were momentous since articles from Canada and Finland were published in Acta Cytologica [8,9] that linked koilocyte-containing condylomas of the uterine cervix to infection by the “wart virus.” It was first shown in 1977 that human papillomavirus (HPV) plays a role in the etiology of squamous cell carcinoma and its precursors [10]. Within a year, speculations about the nature of koilocytes came to an end. Papers from Australia [11] and Italy [12] reported that koilocytes are viral-infected squamous cells and the virus found in the nuclei of koilocytes is consistent with HPV.

In 1981, the first cloning of genital papillomavirus initiated studies that linked koilocytic changes in the uterine cervix to sexually transmitted infection with HPV [13]. By the application of immunohistochemical techniques, molecular cloning of viral DNA by Southern blot analysis, in situ DNA hybridization, and polymerase chain reaction (PCR) amplification, the identification and typing of HPVs was accomplished [14,15]. Viral protein was demonstrated in the nuclei of infected cells in various lesions including anogenital condylomas and carcinomas; cutaneous warts; Bowenoid lesions of the skin; squamous papillomas, and carcinomas of the larynx, trachea, and bronchi [16-21]. It was proven that HPVs are ubiquitous and type-specific for certain organs.

Currently, nearly 100 distinct types of HPVs have been identified, but only a few (eg, HPV 16, 18, 31, and 33) are associated with known neoplastic transformation to squamous cell carcinoma [22]. A prerequisite for malignant transformation of preneoplastic cells (atypical and koilocytic squamous cells) to cancer is persistent, continuous infection. A consensus was recently reached that >90% of cervical squamous cancers and 75% of cervical lesions with koilocytes harbor HPV DNA.

In 2006, the Food and Drug Administration of the United States approved the first vaccine to prevent cervical cancer.

It is fitting to recognize that these accomplishments were achieved by the international cooperation of gynecologists, cytologists, pathologists, virologists, molecular biologists, and the many donors and workers who supported and assisted their efforts.

References