TRANSLATIONAL MEDICINE: A Historical Excursus of Studies Concerning the Cause-and-Effect Relation between Anogenital Warts/Cervical Cancer and the Human Papilloma Virus

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Abstract

The implementation of results and principles of basic sciences into practical medicine is defined as translational medicine. The present review aims to highlight milestone studies that have been focusing on the cause-and-effect relation of anogenital warts and the human papilloma virus. Furthermore, it aims to shed light on the outstanding scientists and physicians who have been passing the baton throughout the ages. Indeed, the impact of basic sciences and scholars on physicians’ routine is not to be underestimated.

Keywords: Translational Medicine; Papillomavirus; Human Papilloma Virus; Skin; Anogenital Warts; Condylomas; Cervical Cancer

Introduction

The implementation of results and principles of basic sciences into practical medicine is defined as translational medicine. History of discoveries concerning genital warts and cervical cancer and attempts to determining the viral origin of these diseases is very obvious case to demonstrate an impact of translational research on our routine. Therefore the present review aims to highlight milestone studies that have been focusing on the cause-and-effect relation of anogenital warts and the human papilloma virus. Furthermore, it aims to shed light on the outstanding scientists and physicians who have been passing the baton throughout the ages. Indeed, the impact of basic sciences and scholars on physicians’ routine is not to be underestimated.

Historical sources concerning warts and its nature

Already in ancient sources, there are records concerning anogenital, mucosal and skin lesions. For example, it is a well-known fact that Hippocrates called genital warts “thymus” [1].

In his manual “De Medicina”, the great Roman scholar Aulus Cornelius Celsus described various skin and mucosal lesions [2]. For his multidisciplinary vision and extensive knowledge he was reputed to be a true encyclopedist and ‘a physician of extraordinary merit’ [3].

Celsius thoroughly described skin and anogenital lesions suggesting that these diseases had a common cause-and-effect relation. He used the term “Acrochordon” for skin warts and noted similarities in clinical manifestations of these lesions with corns and plants “ficus”. Interestingly, large and deep anogenital lesions were called “Myrmecia” (a form of viral wart in which the lesion has a domed surface). Celsius wrote that these have deep roots closely adhering to surrounding tissues. Celsius mentioned that the surgical removal of such kinds of large lesions with deep roots is...
accompanied by bleeding from extended wounds. Physicians have been using the treatment principles for warts described by Celsius for ages: chemical and/or thermal cauterization, and surgical excision [2].

The preconceived hypothesis that sexual intercourse has a causative relation with anogenital warts was developed by ancient Greeks and Romans. In his satires, the Roman poet DecimusJuniusJuvenalis made fun of the morals and manners of his contemporaries by describing the removal of anal condyloma [4]. This is an allusion that anogenital warts were associated with homosexuality.

From the inguinal outgrowth of a renaissance mummy (Maria d’Aragona, Marquise of Vasto, 1503-1568) deposed in the basilica of San Domenico Maggiore in Naples the human papilloma virus (HPV) genotype 18 was identified [5].

### Determining the viral origin of warts

In the 19th- 20th century a concept was developed that sexual intercourse has a causative relation with anogenital warts was developed by ancient Greeks and Romans. In his satires, the Roman poet DecimusJuniusJuvenalis made fun of the morals and manners of his contemporaries by describing the removal of anal condyloma [4]. This is an allusion that anogenital warts were associated with homosexuality.

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### Until the middle of the 20th century, auto-inoculations of extracts from anogenital warts in other patient locations took place with the subsequent development of warts in these locations (see Table 1). Analogous experimental studies were done in animal species such as rabbits, horses, cows and dogs, which suffer from similar wart-like diseases (see Table 1).

Richard E. Shope discovered that the papillomavirus is a cause of horny warts on cottontail rabbits. He proved his hypothesis by subcutaneous and intratesticular inoculation of extracts containing an infection agent. Richard E. Shope applied serial experiments with intratesticular inseminations of wart extracts in order to establish a laboratory model of horny warts on cottontail rabbits. Then he proved the viral origin of the disease by applying special filters. The cottontail rabbit papillomavirus (CRPV) was named the “Shope papilloma virus” and provided the first experimental cancer model in mammalian [6].

#### Table 1. From bench to bedside history of papillomavirus investigation

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of animal and human diseases-induced by papillomavirus</th>
<th>Object (model)</th>
<th>Aim and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCFADYean and Hobday, 1898</td>
<td>Warts</td>
<td>Dog</td>
<td>Transmission</td>
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<tr>
<td>Cirollo, 1907</td>
<td>Warts</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Waelsch, 1917</td>
<td>Condylomacuminatum</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Wile and Kingery, 1919</td>
<td>Warts</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Magalhaes, 1920</td>
<td>Bovine papillomavirus</td>
<td>Bull</td>
<td>Transmission</td>
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<tr>
<td>Lutz, 1922</td>
<td>EDV</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Ullmann, 1923</td>
<td>Laryngeal papilloma</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Serra, 1924</td>
<td>Condylomacuminatum</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Frey, 1924</td>
<td>Warts</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>DeMonbreun and Goodpasture, 1932</td>
<td>Canine oral papillomavirus</td>
<td>Dog</td>
<td>Transmission</td>
</tr>
<tr>
<td>Shope, 1933</td>
<td>CRPV, Shope papilloma virus</td>
<td>Rabbit</td>
<td>Transformation into cancer cells under cancerogenous agents</td>
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<tr>
<td>Parsons and Kidd</td>
<td>Rabbit oral papilloma</td>
<td>Rabbit</td>
<td>Transmission</td>
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<tr>
<td>Cook and Olson, 1951</td>
<td>Horse cutaneous papilloma</td>
<td>Horse</td>
<td>Transmission</td>
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<tr>
<td>Jablonska and Millewsky, 1957</td>
<td>EDV</td>
<td>Human</td>
<td>Transmission</td>
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<tr>
<td>Goldschmidt amd Kligman, 1958</td>
<td>Warts</td>
<td>Human</td>
<td>Transmission</td>
</tr>
<tr>
<td>Ito &amp; Evans, 1961</td>
<td>Purified DNA CRPV</td>
<td>Rabbit</td>
<td>Induction of squamous cell carcinoma</td>
</tr>
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<td>Black et al, 1963</td>
<td>BPV</td>
<td>in vitro</td>
<td>Transmission</td>
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<tr>
<td>Thomas et al, 1963</td>
<td>BPV</td>
<td>in vitro</td>
<td>Identification of agent and transmission</td>
</tr>
<tr>
<td>Orth et al, 1977 - 1979</td>
<td>HPV in EDV</td>
<td>in vitro</td>
<td>Identification of agent and transmission</td>
</tr>
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<td>zurHauen et al, 1974-1977</td>
<td>HPV and cervical cancer</td>
<td>in vitro</td>
<td>Identification of DNA in condylomas and cervical cancer HPV heterogeneity</td>
</tr>
<tr>
<td>Gissmann &amp; zurHausen, 1977</td>
<td>HPV, condyloma and cervical cancer</td>
<td>in vitro</td>
<td>Interpretation of koylocytosis as HPV consequences</td>
</tr>
<tr>
<td>Meisels and Fortin, 1976; Meisels et al, 1977; Purola and Savia, 1977</td>
<td>HPV, condyloma and cervical cancer</td>
<td>in vitro</td>
<td>Identification of agent and transmission of host cells</td>
</tr>
<tr>
<td>Lowy et al, 1980</td>
<td>HPV, condyloma and cervical cancer</td>
<td>in vitro</td>
<td>HPV genome as transforming agent of host cells</td>
</tr>
<tr>
<td>Gissmann and zurHausen, 1980</td>
<td>Genital condylomas</td>
<td>in vitro</td>
<td>HPV6</td>
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<tr>
<td>Chen et al, 1982</td>
<td>BPV</td>
<td>in vitro</td>
<td>Complete BPV1 genome sequencing</td>
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<tr>
<td>Gissmann et al, 1982</td>
<td>Laryngeal papillomatosc</td>
<td>in vitro</td>
<td>HPV11</td>
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<tr>
<td>Durst et al, 1983</td>
<td>Cervical cancer</td>
<td>in vitro</td>
<td>HPV16 was cloned</td>
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<tr>
<td>Boshart et al, 1984</td>
<td>Cervical cancer</td>
<td>in vitro</td>
<td>HPV18 was cloned</td>
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<tr>
<td>Schwarz et al; Yee et al, 1985</td>
<td>Carcinoma tissue</td>
<td>in vitro</td>
<td>Expression of E6 and E7</td>
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</table>

Richard E. Shope involved Peyton Rous in his papillomavirus research. Earlier, Rous had discovered the 'Rous sarcoma virus' (Nobel Prize in 1966) with his theory that cancer could indeed be transmitted by a virus [7]. Subsequently, Peyton Rous and his coworkers discovered a possibility to converse the papillomavirus into intermediate (pre-cancer) then cancer cells upon exposure to cancerogenous factors [8-10].

Long-lasting experimental studies in the 20th century demonstrated that HPV is a multidisciplinary problem since it seems to be an etiologic factor of skin, oral and anogenital warts, as well as neoplasia and cancer.

Findings concerning HPV and related neoplastic processes are completely in line with the analogous criteria of Koch's postulates: HPV was isolated from its host; virions could be cultivated in keratinocytes culture; a viral infectivity remained after bacterium filtration; induction of the disease was proved by inoculations in patients and in experimental models.

**Determining the viral origin of cervical cancer**

Between 1760 and 1839, the first epidemiological investigation of cervical cancer was a statistical incidence analysis of cancer-related mortality in nuns and unmarried women as compared to married women. It was conducted by the Veronese surgeon Domenico Antonio Rigoni-Stern. He demonstrated that uterine cancer was common in married women but rare in nuns and unmarried women and concluded that sexual intercourse had a causative impact on the development of cancer in married women [11].

The cornerstone changes in cervical cancer prevalence, screening and diagnosis can be traced back to the great scholar Georgios N Papanicolaou, who started cytopathology studies of vaginal smears in the 20s of the last century [12].

Georgios N Papanicolaou spent a quarter of a century establishing an early cancer detection assay. Upon the publication in 1941 of Papanicolaou’s research results entitled “The diagnostic value of vaginal smears in carcinoma of the uterus”, his valuable invention, the «Pap smear», was approved [13]. His findings were published in a monumental monograph book with conclusive results showing that cytological investigation of vaginal smear could identify cervical and uterine cancer prior to the manifestation of cancer symptoms.

In 1943, “Diagnoses of Uterine Cancer by the Vaginal Smear” broke the skepticism of his contemporaries [14]. The Pap test was now accepted. With the organization of the first national cytology conference in Boston in 1948 it became a routine screening technique in the medical communities A classic manual ‘Atlas of Exfoliative Cytology’ by Georgios N Papanicolaou was published in 1954 by Harvard University Press for the Commonwealth Fund [15].

Thanks to the Pap smear, cervical cancer rate dramatically decreased up to 70% in countries where cytologic screening was applied on a large scale, saving millions of lives. However, the author died in 1962, 6 months after having been nominated for the Nobel Prize for the second time.

In 1956 Koss &Durfee used the term “Koilocytoticatypia”
for the first time in order to define a “group of atypical epithelial lesions characterized mainly by the presence of large cells with vacuolated cytoplasm because of the cavitary appearance of the cytoplasm” [16]. Later, koilocytes were interpreted as consequences of HPV infection.

In 1949, crystal-like viral particles from skin warts were scanned owing to the development of optical techniques and laboratory equipment [17].

Drastic changes in HPV biology investigation were associated with the development of molecular medicine tools and assays after dideoxy sequencing, other discoveries in both genetics and molecular biology and the worldwide development of basic sciences in general. So, Ito and Evans (1961) induced tumors in domestic rabbits by means of nucleic acid preparations from a partially purified Shope papilloma virus and from extracts of the papillomas of domestic and cottontail rabbits. Structures and manifestations: spontaneous regression and malignancy in the development of squamous cell papilloma were identical with those in wild cottontail rabbits [18].

Due to the application of polymerase chain reaction (PCR) and other state-of-the-art technologies, revolutionary reconsiderations of cause-and-effect relations of many diseases, including anogenital warts and cervical cancer, have sprung up. PCR assaying has allowed setting up large-scale epidemiological international studies evaluating cervical biopsy samples by amplification of DNA and HPV genotype identification [19-21].

Finally, the role of HPV in the development of cervical intraepithelial neoplasia and cancer was established. DNA HPV was identified in swine papillomas (BPV1), then in human warts and condylomas (HPV6 and HPV11). In research, a BPV system has become the classic prototype of papilloma viral genome. HPV16 and HPV18 were cloned from cervical cancer biopsy. It proved that HPV is a heterogenous virus. It is expected that more than 200 of HPV genotypes will be determined [22]. Today more than 100 HPV types have already been completely identified.

**Breakthrough stages in unraveling the nature of the HPV and its clinical manifestations and consequences**

By identifying the viral genomic structure and principles of its function, signaling pathways of intracellular changes due to the activity of HPV were elaborated. HPV activity led either to the development of cervical intraepithelial neoplasia with progression of the disease or spontaneous elimination of HPV with complete cure. Breakthrough findings include the elaboration of the expression of early and late HPV proteins and the understanding of their functions (Table 1) with HaraldzurHausen being a research initiator in this field [22,23]. Subsequently, HaraldzurHausen and his team, amongst others, identified more than 100 HPV genotypes many of them cloned. The transformation of epithelial cells with stem cell behavior was established with the expression of proteins E6 and E7. Cross talk between HPV proteins E6/E7 and important vital molecules of infected cells such as pRb and p53, which control apoptosis and proliferation signaling pathways in these cells, were demonstrated. These findings have proved that proteins E6 and E7 are associated with the development of malignant phenotypes of infected cells and the further manifestation of cervical cancer. In 2008, HaraldzurHausen was justifiably awarded the Nobel Prize «for his discovery of HPV causing cervical cancer».

The design of HPV vaccines and their wide application, together with new diagnostic and screening assays, have opened new horizons in preventing cervical and other HPV-related cancers.

In conclusion, in this review we have highlighted milestone studies focusing on the cause-and-effect relation of anogenital warts, cervical cancer and the human papilloma virus and have shed light on the outstanding scientists and physicians who have been passing the baton throughout the ages.

**Abbreviations**

BPV: Bowine Papillomavirus;
CRPV: Cottontail Rabbit Papilloma Virus;
HPV: Human Papillomavirus;
DNA: Deoxyribonucleic Acid;
EDV: Epidermodysplasiaverruciformis;
E6 and E7: Early HPV Genes and Proteins;
p53: Tumor Suppressor Gene and Protein;
Pap: Papanicolaou (Pap-test);
PCR: Polymerase Chain Reaction;
pRb: The Retinoblastoma Protein

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Disclosure

The author reports no conflicts of interest or financial ties to disclose. The author alone is responsible for the content and writing of the paper.

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