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Mini Review

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 Celsius 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" (aformofviralwartinwhichthelesionhasadomedsurface). Celsus 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 proved the viral origin of warts (Table 1).

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 papilloma virus (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

Авторы	Type of animal and human diseases-induced by papillomavirus	Object (model)	Aim and outcome
McFadyeanandHobday, 1898	Warts	Dog	Transmission
Ciuffo, 1907	Warts	Human	Transmission
Waelsch, 1917	Condylomaacuminatumn	Human	Transmission
Wile and Kingery, 1919	Warts	Human	Transmission
Magalhaes, 1920	Bovine papillomavirus	Bull	Transmission
Lutz, 1922	EDV	Human	Transmission
Ullmann, 1923	Laryngeal papiloma	Human	Transmission
Serra, 1924	Condylomaacuminatumn	Human	Transmission
Frey, 1924	Warts	Human	Transmission
DeMonbreun and Goodpasture, 1932	Canine oral papillomavirus	Dog	Transmission
Shope, 1933	CRPV, Shope papilloma virus	Rabbit	Identification of agent and transmission
Rous et al, 1936 - 1944	CRPV	Rabbit	Transformation into cancer cells under cancerogenous agents
Parsons and Kidd	Rabbit oral papilloma	Rabbit	Transmission
Cook and Olson, 1951	Horse cutaneous papilloma	Horse	Transmission
Jablonska and Millewsky, 1957	EDV	Human	Transmission
Goldschmidt amdKligman, 1958	Warts	Human	Transmission
Ito & Evans, 1961	Purified DNA CRPV	Rabbit	Induction of squamous cell carcinoma
Black et al, 1963	BPV	in vitro	Transmission
Thomas et al, 1963	BPV	in vitro	Transmission
Orth et al, 1977 - 1979	HPV in EDV	in vitro	Identification of HPV5
zurHauzen et al, 1974-1977	HPV and cervical cancer	in vitro	Identification of DNA in condylomas and cervical cancer HPV heterogenocity
Gissmann&zurHausen, 1977			
Meisels and Fortin, 1976; Meisels et al, 1977; Purola and Savia, 1977	HPV, condyloma and cervical cancer	in vitro	Interpretation of koylocytosis as HPV consequences
Lowy et al, 1980	HPV, condyloma and cervical cancer	in vitro	HPV genome as transforming agent of host cells
Gissmann and zurHausen, 1980	Genital condylomas	in vitro	HPV6
Chen et al, 1982	BPV	in vitro	Complete BPV1 genome sequencing
Gissmann et al, 1982	Laryngeal papillomatose	in vitro	HPV11
Durst et al, 1983	Cervical cancer	in vitro	HPV16 was cloned
Boshart et al, 1984	Cervical cancer	in vitro	HPV18 was cloned
Schwarz et al; Yee et al, 1985	Carcinoma tissue	in vitro	Expression of E6 and E7

Lewandowsky and Lutz, 1922	Described hereditary syndrome of extensive manifestation of EDV	
Frey, 1924	Suggested a hypothesis that skin and anogenital warts have the same origin	
Fabru W, 1614	Giant condyloma was initially described	We fully agree with suggestion by Marx and Karenberg (2012)that "Fabry's is the first clinical report; the histological classification, belongs to Buschke and Löwenstein. The disease should be designated with the eponym Giant condyloma of Fabry-Buschke-Löwenstein".
Buschke and Loewenstein, 1925	Then it was again described by Buschke and Loewenstein including histological features of the disease. Then it was named as "Buschke-Löwenstein tumor"	
Papanicolaou, 1928, 1941, 1943, 1954	Typical for HPV cyto-morphological changes were described the first time at all. These were basics for Pap-test which is the basic tool for cervical cancer screening.	
Strauss et al,1949	Crystalloid viral particles were identified under scanning electron microscopy	
Koss and Durfee, 1956	The term "koilocytocytoticatypia" was used	
zurHauzen, 1970s	Forwarded a hypothesis that HPV is a cause of cervical cancer	

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]. Subesquently, Peyton Rous and his coworkers discovered a possibility to converse the papillomavirus into intermediate (precancer) 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 angenital warts, as well as neoplasia and cancer.

Findings concerning HPV and related neoplastic processes are completely in line with the analogeous criteria of Koche'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 иHPV11). 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 heterogenic 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.

References

1. Adams F. The Genuine Works of Hippocrates, Translated from the Greek with a Preliminary Discourse and Annotations by Francis Adams, LL.D., Surgeon. In Two Volumes. New York. 1886.

2. Celsus AC. De Medicina, book 5, chapter 28, section 14. Around 25 AD.

3. Aulus Cornelius Celsus Biography (c25 B.C.-c50). Dove Medical Press.

4. Bafverstedt B: Condylomataacuminata-past and present. Acta Derm Venereol (Stockh), 1967; 47: 376-381.

5. Fornaciari G. The Aragonese mummies of the Basilica of Saint Domenico Maggiore in Naples. Med Secoli. 2006, 18(3): 843-864.

6. Shope RE, Hurst EW. Infectious papillomatosis of rabbits: with a note on the histopathology. J Exp Med. 1933 Oct 31; 58(5): 607-624.

7. Rous P. A sarcoma of the fowl transmissible by an agent separable from the tumor cells. J Exp Med. 1911, 13(4): 397-411.

8. Rous P, Kidd JG. The activating, transforming, and carcinogenic effects of the rabbit papilloma virus (shope) upon implanted tar tumors. J Exp Med. 1940, 71(6): 787-812.

9. Rous P, Friedewald WF. The effect of chemical carcinogens on virus-induced rabbit papillomas. J Exp Med. 1944, 79(5): 511-538.

10. Rous P, Friedewald WF. The carcinogenic effect of methylcholanthrene and of tar on rabbit papillomas due to a virus. Science. 1941, 94(2447): 495-496.

11. Griffiths M: Nuns, virgins, and spinsters. Rigoni-Stern and cervical cancer revisited. Br J Obst Gynaecol. 1991, 98: 797–802.

12. Papanicolaou G.N. Atlas of Exfoliative Cytology Cambridge, Mass.: Harvard University Press. 1954.

13. Papanicolaou G.N. New cancer diagnosis. Proc of the 3rd Race Betterment Conference. Battle Creek, Michigan, RBF. 1928, 528-534.

14. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smear in carcinoma of uterus. Am J Obstet Gynecol. 1941, 42: 193-205.

15. Papanicolaou GN, Traut HF. Diagnosis of Uterine Cancer by the Vaginal Smear. New York, Commenwealth Fund. 1943, 46.

16. Koss LG and Durfee CR. Unusual patterns of squamous epithelium of the uterine cervix: Cytologic and pathologic study of koilocytoticatypia. Ann. N. Y. Acad. Sciences. 1956; 63: 1245-12126.

17. Strauss MJ, Shaw EW, Bunting H, Melnick JL. Crystalline virus-like particles from skin papillomas characterized by intranuclear inclusion bodies. Proc Soc Exp Biol Med. 1949, 72(1): 46-50.

18. Ito Y, Evans CA. Induction of tumors in domestic rabbits with nucleic acid preparations from partially purified shope papilloma virus and from extracts of the papillomas of domestic and cottontail rabbits. J Exp Med. 1961, 114(4): 485-500.

19. Bosch FX1, Manos MM, Muñoz N, Sherman M, Jansen AM et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst. 1995, 87(11): 796-802.

20. Alemany L, de Sanjosé S, Tous S, Quint W, Vallejos C et al. Time trends of human papillomavirus types in invasive cervical cancer, from 1940 to 2007. Int J Cancer. 2014, 135(1): 88-95.

21. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomisedcontrolled trials. Lancet. 2014, 383(9916): 524-532.

22. zurHausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst. 2000, 92(9): 690-698.

23. zurHausen H. [Virus induced oncogenesis]. Med Welt. 1970, 47: 2020-2023.