

## From the humble wart to HPV: a fascinating story throughout centuries

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Nowadays human papillomavirus (HPV) is a significant source of morbidity and mortality worldwide. Epidemiological studies suggest that 75% of all sexually active people will become infected at some point during their lifetimes [1].

Condylomata acuminata, was a well-known disease at least from the time of Hippocrates (460–370 BC) [2]. Concerning the etymology, the term *condyloma* derives from ancient Greek and means a round tumor and *acuminata* comes from the Latin for “sharp points”. Myrmecia, a term applied to plantar warts is derived from the Greek word for anthill. In Roman period genital warts were referred to by the terms “ficus” meaning fig because of its resemblance of an open fig and “thymus” from the greek *thymion* because they looked like the leaves of the plant thyme [3, 4]. A term appeared also in the writings of the Byzantine physician Aetius of Amida (sixth century BC) that mentions: “The term thymus arises from the similarity to the tips of the plant of the same name, which grows in the mountains...It appears in the anus and the pudenda and between the legs” [5]. The term verruca was first used by

the German physician Daniel Sennert (1572–1637). In his book entitled *Hypomnemata physicae* (1636) he points out that they appear on the surface of the skin like the eminences of little hills [6].

At the beginning of the first century AD the Roman physician Aulus Cornelius Celsus in his book *De Medicina* described three morphologically distinct types of cutaneous warts: (1) the acrochordon which appeared exclusively in children and undergone frequently a spontaneous resolution; (2) the thymion which was a papillomatous and highly vascular lesion that could be developed in the genitalia; and (3) the myrmecia currently known as plantar warts [7]. In ancient Rome it was believed that warts were the result of promiscuous sexual behavior and many satirical poems were written as those in the books *Epigrams* of the Latin poet Martial (first century AD) [8].

Condylomata acuminata survived the middle ages; in the writings of Lanfranchi (thirteenth century) and Guglielmo da Saliceto (1210–1277) we can find descriptions of genital warts [9]. However, theories about their causation abounded, giving rise to many controversies. The outbreak of syphilis in Europe, at the end of fifteenth century, gave a new interest to genital diseases. Many genital infections as syphilis, gonorrhoea and warts were attributed to the same “venereal poison” so well defined centuries later by John Hunter (1728–1793): “The venereal disease arises from a poison which it is produced by the disease and it is capable of again producing a similar disease...it has different powers of contamination...when it is applied to the human body it possesses a power of propagating or multiplying itself” [10]. The “venereal poison” theory led many physicians, including Hunter to regard anogenital warts as a manifestation of syphilis.

In 1712 Daniel Turner (1667–1741), the author of the first book in the English language devoted to dermatology,

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entitled *De morbis cutaneis*, gives his own explanation for the cause of warts as he believes that they might be “congealed nutritious juices” that had passed from damaged nerve filaments in the skin [11].

The first to recognize that warts comprised a disease entity unrelated to syphilis was the Scottish surgeon Benjamin Bell (1749–1806). Furthermore, he was among the first to describe the appearance of anal cancer in a pre-existing condylomatous lesion as he stated: “I have at present a person who had long been liable to piles, who some time ago was attacked with condylomatous excrescences from a venereal taint; to these succeeded a common abscess from inflammation, and last of all the parts have become cancerous” [12].

By the time the idea that correlated warts and syphilis was abandoned and replaced by another erroneous view that linked warts to gonorrhoea as nineteenth century physicians’ observed that condylomata usually appeared at the end of an attack of gonorrhoea and so they called them “gonorrhoeal warts”. However, it is interesting to mention the evolutionary study of Domenico Rigoni-Stern (1810–?), chief physician of a hospital in Verona: on analyzing the death certificates due to cancer in Verona during the period 1760–1839, he found that deaths due to cervical cancer were very rare among virgins and nuns in contrast to married women and widows, linking for the first time cervical cancer with sexual diseases [13].

In the same period some strange suggestions concerning the etiology of warts were made. In 1849, *Lancet* published an article under the title *Peculiar sign* describing that “Dr Durr maintained, many years ago, in Hufeland’s *Journal* that females addicted to solitary habits (meaning masturbation) often present with warts on the index or middle finger. Dr Kretschmar, to corroborate this remark, related that a girl, accustomed to search for the near laying of eggs by introducing the index finger into the cloaca of hens, had many warts on that finger” [14]. Also the Viennese dermatologist Ferdinand von Hebra (1816–1880) mentioned in 1874 various other theories concerning warts’ etiology as association with animals, repeated irritation of the epidermis, genital discharges, decomposed sebaceous material and he concluded that the “influences causing warts are still very obscure” [15]. In 1879, Albert Neisser (1855–1916) discovered gonococcus, the pathogenic agent of gonorrhoea and it became clear that many patients with condylomata showed no signs of gonorrhoeal infection, putting end to the idea that linked warts to gonorrhoea.

The work of Joseph Payne, physician at Saint Thomas Hospital, London, contributed further to the understanding of the contagious nature of common warts. In a paper published in 1891 he described how he developed a wart on his thumb 1 week after scraping lesions from an 11-year-old boy with skin warts; he stated that “common warts

appear to arise by the implantation of some contagious material at one or more points of the skin” and he concluded that the etiology of condylomata acuminata and common warts converged [16].

A turning point in the long disputes over etiology was reached in 1893 when the French dermatologist Gémy suggested that condylomata acuminata and common skin warts might be caused by the same pathological agent as there were histological resemblances and many patients with genital warts had warts in their hands [17]. In the following years experiments on the contagiousness began and in 1894 evidences were supplied simultaneously by C. Licht and the Parisian pediatrician Gaston Variot (1855–1930). Licht [18] inoculated material from a wart into his own skin and successfully produced a wart and Variot [19] inoculated the finger of his assistant with fluid from a wart and produced a new lesion.

In 1901, M.L. Heidingsfield linked the oral condylomas with the genital ones. He reported the case of a 24-year-old “puella publica” who was suspected of acquiring genital warts of the tongue as a result of “coitus illegitimus” (oral sex). Heidingsfield performed detailed histological studies of the wart specimens from both the tongue and labia of his patient and concluded that condylomata acuminata of the lips conforms not only in clinical character but also in histological structure to condylomata acuminata of the genital location [20].

In 1907 Dr. Giuseppe Ciuffo demonstrated the viral nature of genital warts by inoculating successfully to the skin, a wart extract that had been filtered through a pore size small enough to exclude bacteria and fungi but not viruses (Berkefeld filter). This suggested that the infecting agent might be a virus and indicated a way of transmission, the inoculation. Ciuffo’s [21] results were enough to convince the researchers that the genital warts were not only caused by a virus but this virus was identical to that which caused common warts.

In the following decades a number of major breakthroughs in many aspects of warts research have occurred as the appearance of HPV particles in skin warts [22], the concept of koilocytosis in Pap smears and cervical biopsies [23], the discovery of human papova group [24, 25], the electron microscopic demonstration of HPV particles in genital warts [26, 27], the description of koilocytic atypia as a sign of HPV in flat lesions of the cervix [28, 29] and finally the leading discovery of the German virologist Herald zur Hausen (1936–). In 1976, he published the hypothesis that human papilloma virus plays an important role in the cause of cervical cancer [30] and then in 1983 he identified the types HPV16 and HPV18 [31]. A revolutionary work that made possible the development of HPV vaccine, introduced in 2006. For his research zur Hausen received the Nobel Prize in Physiology or Medicine 2008.

Throughout centuries science has made a remarkable progress both in clinical and therapeutical fields in the study of HPV, a major cause of human pathology. Nowadays concerns have to focus mainly on prevention measures (Pap test, sexual education, vaccination) in order to limit the spread of this highly virulent virus.

**Conflict of interest** None.

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