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W A R T S

by

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Most discussions of warts emphasize their benign behavior; this review will point to situations, however uncommon, in which they may become malignant. Warts are often considered to parasitize only the epidermis. In fact, they may flourish upon oral, genital, respiratory and rectal mucosa. Despite the disability caused by plantar and anogenital warts, the Social Security Administration until this year considered them so trivial a problem that Medicaid refused to reimburse providers for their treatment.

PREVALENCE

The frequency of warts varies considerably among different populations but seems to be increasing in many western European countries, and perhaps in the United States. Warts of all types now account for 10 to 25% of new patients at some British clinics as compared with 3 or 4% 30 years ago (1). School medical inspectors in Cambridge, England, found that 6.5% of children had plantar warts and 9.7% other types (2). They found plantar warts more common in girls than in boys after age 6. Another survey in Holland found 7.2% of children affected overall (3). Approximately the same figures seem likely to hold for the U.S. The peak ages for ordinary warts fall between 12 and 16. Thereafter the prevalence falls sharply to age 20 and more gradually as age increases. For mucosal warts the peak coincides with the years of peaks for other venereal diseases.

EPIDEMIOLOGY

Warts are transmitted by direct or indirect contact with human carriers, although the long and variable incubation period (1 to 6 months) has confused and misled investigators. The literature is filled with anecdotes concerning transmission of warts (reviewed in 4). As an example, one outbreak involved women who glued cardboard boxes together in a small factory (6). Eleven of 21 workers directly touched the glue. These 11 had warts while the others did not. The glue was made fresh daily and heated to 80°C, but used after it had cooled, at which time handling by infected workers led to its contamination by virus. To prove the source, the investigators painted uninfected individuals with glue. These subjects developed warts if the glue pot had been used by infected workers, but did not if the glue was prepared in the lab (using the same materials) but had not contacted those with warts.

TABLE I

Main Characteristics of Human Lesions
Known to be Associated with a Papillomavirus

Clinical types	*Viral content*	*Age distribution*	*Natural transmission*	*Predisposing factors*	*Malignant transformation*
Skin warts (common, plantar, flat, filiform types)	variable, usually high	children, young adults	direct or indirect contact through minor abrasions	community life, immune deficiency	not reported (usual regression)
Epidermodysplasia verruciformis	moderate	lifelong growth	unknown	genetic factors	frequent (no regression)
Condylomata acuminata (anal, genital warts)	low	young adults	mainly venereal	sexual promiscuity, poor hygiene, pregnancy	rare (vulva, penis, anus)
Oral papillomas	low (one report)				
Oral focal epithelial hyperplasia	moderate	all age groups	unknown	genetic factors	not reported
Juvenile laryngeal papillomatosis	extremely low, if any	infants and children, adults	at delivery or unknown	mothers with condylomas, presence of skin warts (?)	rare (recurrent, persistent lesions)

(From Ref 23)

CLASSIFICATION

Morphologically warts are classified either by appearance or location. These descriptive terms remain useful despite abundant evidence (summarized below) a single wart virus can cause two or more morphologic types of warts. Many investigators have shown further that wart extracts taken from one anatomic site and injected into a remote site will produce warts typical of the site of injection rather than the site of origin.

1) The ordinary wart (verruca vulgaris) is a firm papule with a rough, horny surface. Single warts range in size from sub-millimeter to over a centimeter. By confluence with other warts they can form large masses. The ordinary wart most often affects the dorsal hands and fingers. Multiple warts (difficult to treat!) are often found around the nail in nail-biters, and new ones seem particularly to prefer sites of trauma. Common warts may cause pain on the palmar aspect of the fingers, may disturb nail growth if they encroach upon them, and may rarely cause conjunctival or corneal irritation on the eyelids.

2) Plantar warts cause the greatest economic hardship. As a result of the constant pressure of walking they expand within the substance of the foot rather than outward from it. Due to the thick plantar stratum corneum around it, a plantar wart rolls up a ring or collar of horn around itself, a ring which can easily be distinguished from the central wart when pared. Other features which distinguish a wart from a corn or callus include: 1) small bleeding points, the tips of dermal papillary vessels, revealed with further paring and 2) the fact that the epidermal ridges are not continued over the surface of warts.

Most affected individuals have one or at most a few plantar warts, usually located over pressure points. But in a minority there may be a cluster of satellites or a single large plaque. This plaque may appear to represent one wart until pared, when the removal of overlying tissue displays the close grouping of multiple individual warts with their angular, mosaic outlines.

This tendency to produce multiple rather than large single warts has become easier to interpret since work with enzymatic markers (6,7) has indicated that most human warts represent a clonal expansion of a single viral-infected cell.

3) Flat or plane warts display a smooth, flat-to-slightly-elevated appearance with a light brown or grayish-yellow cast in most individuals. The face, dorsal hands, and shins appear most vulnerable. This type of wart may present unusually large numbers of lesions -- from a few to thousands. One often sees a contiguous line of flat warts in an apparent scratch mark. A few ordinary warts may occur in the same patient but this mixture of types is uncommon.

When flat warts develop extensively and rapidly in infancy or childhood and remain persistent for decades the term epidermodysplasia verruciformis or generalized verrucosis is applied (8). The familial occurrence of this syndrome which may rest on an immune deficiency state (9) has intrigued investigators. Generalized verrucosis will be considered in more detail below since it represents the only human disease in which an oncogenic DNA virus regularly produces malignancy in man.

4) Filiform warts occur as delicate pointed projections 1 to 3 mm long, usually on the neck or face and with special frequency on the eyelids, lips, and nose.

5) Mucosal warts (condyloma acuminatum, condyloma = from Latin and Greek roots meaning joint, knuckle, or fist. Something knobby is suggested. acuminatum = from Latin meaning pointed or sharpened) are also known as venereal or moist warts. Besides the anogenital region they may affect the urethra (10), vagina (11), rectal mucosa (12), mouth (13), larynx (14), and rarely bronchi (15). From epidemiologic studies genital warts appear to spread in a venereal pattern and to occur with highest prevalence among male homosexuals (16).

Although oral papillomas represent one of the most frequently encountered lesions of the mouth, only a single isolated report (17) suggests they may contain wart virus.

Warts in the larynx may occur at any age (14) but present serious problems in young children who may contract them during delivery through an infected birth canal (18,19). Early in the course, airway closure can be prevented by tracheostomy but spread of lesions to the bronchi may cause death by suffocation.

Pregnancy and birth-control pills appear to stimulate growth and extension of genital warts, some of which may then regress spontaneously at the time of delivery.

Condylomata often respond to local treatments but occasionally prove resistant and grow to large size. The rare giant genital condyloma has the appearance clinically of a malignant tumor but remains histologically benign. This form may cause multiple uretural or anal fustulae and tenaciously resist conservative therapy (20,21).

MICROSCOPIC FINDINGS (22)

Ordinary and plantar warts display thickening of all layers of the epidermis with long flattened dermal papillae which bend inward in apparent radial arrangement toward the center. The most useful feature for differentiating warts from other papillomas is the presence of vacuolated cells in the granular layer and upper prickle cell layer. When treated with tritium-labelled RNA complementary to wart virus DNA and viewed with autoradiography the round, deeply basophilic nuclei in these vacuolated cells were found to contain large numbers of virus particles (23). The immunoperoxidase technique using light or electron microscopy yielded similar intranuclear localization of virus, along with lesser cytoplasmic staining (24).

Flat warts differ in microscopic appearance from ordinary ones. Instead of displaying long dermal papillae, flat warts show only modest, plate-like epidermal thickening and a loose, basket-weave hyperkeratosis.

Since mucosal warts occur on non-cornifying epithelia, only the nucleated layers become thickened. Vacuolated cells are less frequent in such condylomata while the underlying connective tissue often appears very edematous and vascular. The differentiation between a benign but clinically aggressive condyloma and a verrucous carcinoma destined eventually to kill the patient can be a difficult one (25).

THE WART VIRUS

Human wart virus (human papilloma virus or HPV) belongs to the papilloma virus group of the papova virus family. This group contains at least 13 different members affecting nine species of mammals and one of birds (23).

TABLE II

Pathogenicity of Animal Papillomaviruses

Natural infection		*Experimental infection*		
			In alien hosts	
host species	*pathogenicity*	*in natural host (pathogenicity)*	*species*	*pathogenicity*
Chaffinch	skin papillomas	not demonstrated		
Opossum	skin papillomas	not demonstrated		
Cottontail rabbit (*Sylvilagus floridanus*)	skin papillomas and carcinomas	natural disease	domestic rabbit, members of gen. *Lepus*	skin papillomas and carcinomas
Dog	skin papillomas	not demonstrated		
Horse	skin papillomas	natural disease		
Domestic rabbit (*Oryctolagus cuniculus*)	oral papillomas	natural disease	cottontail rabbit, members of gen. *Lepus*	oral papillomas
Dog	oral papillomas	natural disease		
Chimpanzee	focal hyperplasia of oral mucosa			
Cattle	oral, esophageal, and ruminal papillomas	natural disease		
Cattle	skin and genital fibropapillomas	natural disease, ningiomas, polypoid amors of urinary bladder	mouse, hamster, pika, domestic rabbit, horse	connective tissue benign or malignant tumors
Sheep	skin fibropapillomas	natural disease	hamster	fibromas
Deer	skin fibromas	natural disease	hamster	fibromas

(From Ref 23)

In recent years biochemical and structural studies have extended our detailed knowledge of wart virus. Virus can be purified from wart tissue by mincing and grinding in a mortar and pestle with sand or carborundum. Debris and abrasives settle out on low-speed centrifugation while virus particles can be pelleted by high-speed spinning, then purified by their band-like distribution on density-gradient centrifugation. The whole virus can then be viewed by the electron microscope (26), or their components can be studied separately.

The viral DNA can be separated from its coat proteins by detergent treatment (27). Several tricks can be used to compare the sequences of the DNA from, say, plantar warts and genital warts without actually determining what those sequences are. The separate DNA samples can be treated with enzymes called restriction nucleases that cleave the macromolecule at specific sites. The resulting patterns of fragmentation can be compared and tabulated. RNA that is complementary to one sample of DNA can be synthesized in vitro using tagged precursors. That cRNA or comparably produced matching DNA will hybridize or anneal with matching DNA under certain conditions and can be used to fish for similar sequences in the second DNA sample. The coat proteins can be fractionated by electrophoresis (28) or characterized indirectly by the antibodies they elicit in experimental animals (29).

Papillomaviruses differ from other groups within the papova virus family by displaying slightly larger size -- 55 nm diameter for their icosahedral capsid instead of 45 nm for polyoma -- and slightly heavier DNA -- 5.10^6 Daltons instead of $3.6.10^6$. The DNA is double stranded. Only enough is present to code for proteins with a combined molecular weight of a few hundred thousand. All papovaviruses are ether-resistant DNA viruses with tumor-producing properties. The SV-40 agent which is definitely known to transform non-lymphoid human cell lines, is one member of the family, as is the agent (JVC virus) of progressive multifocal leukoencephalopathy (PML) (30) and another new papova virus (BK virus) isolated from urine of immunosuppressed renal transplant recipients (31).

In 1907 HPV was the first tumor-inducing virus shown to be active in cell-free preparations (32). An Italian worker produced a wart on his own hand using a wart extract he had passed through a bacteria-proof filter. Since then many experimental transmissions have been accomplished. In summary, these reports emphasize (Table III): 1) The variability of the incubation period and its lack of dependence on dose of virus used; 2) The unexplainable resistance of some human hosts; 3) The lack of success of experimental transmission to other species; and 4) The possibility of producing ordinary warts from material derived from condylomata and vice versa.

TABLE III

Summary of Experiments on the Transmission of Human Warts in Man

Investigator	Year	Source of virus prepn	Filter[a]	Inoculation site	No. of subjects		Incubation period
					Injected	Developing warts	
							months
Licht (84)	1894	Wart on finger	N. F.	Hand and arm	1	1	6
Variot (146)	1894	Wart on hand	N. F.	Finger	2	1	3
Jadassohn (74)	1896	Warts on back and arms	N. F.	Hand	6	6	2
Lanz (82)	1899	Wart on hand	N. F.	Hand	1	1	1.5
Ciuffo (29)	1907	Warts on hand	B. N.	Finger	1	1	5
Serra (125)	1908	Condylomata	B. W.	Genitalia	4	0	
				Arm, hand	3	0	
		Warts on head	B. W.	Genitalia	2	0	
				Head, hand	3	0	
		Warts on hand	B. W.	Genitalia	1	0	
				Head, hand	4	2	6
Tuccio and Coppolino (142)	1912	Warts on neck	N. F.	Upper arm	6	4	2–6
Merian (104)	1913	Warts on hand	N. F.	Hand	1	1	2.5
Waelsch (148)	1918	Condylomata	N. F.	Genitalia	1	1	3
				Arm	2	2	3–10
Wile and Kingery (155)	1919	Fresh warts	B.	Hands	3	3	1–2
		Glycerine-preserved warts	B.	Hands	2	0	
		Normal skin	B.	Hands	1	0	
Kingery (76)	1921	Filtrate-induced warts	B.	Hands	1	1	6
Ullman (143)	1923	Laryngeal warts	N. F.	Arm, face, and scalp	8	4	3
		Filtrate-induced warts	N. F.		1	1	1
		Filtrate-induced warts	+	Arm, buttock	2	2	
Serra (126)	1924	Condylomata	C.	Genitalia, hand, and foot	7	1	
		Suprapubic wart	C.	Genitalia and hand	3	2	5
Templeton (141)	1935	Skin warts	B. N.	Arm	6	2	12–20
Ishikawa (72)	1936	Laryngeal warts	N. F.	Arm	1	1	3
Lyell and Miles (90)	1951	Warts on hand	N. F.	Arm	11	4	5–12
Goldschmidt and Kligman (52)	1958	Condylomata	N. F.	Various	7	7	3–6
		Warts on face	N. F.	Various	36	1	3

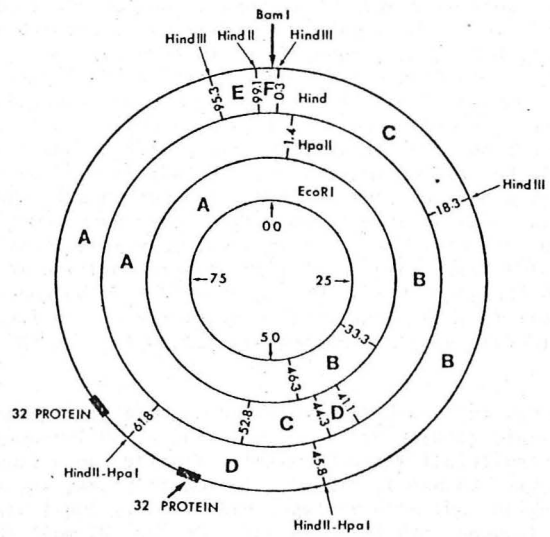
[a] N. F., not filtered; B. N. and B. W., filtered through a Berkefeld N or W filter; C., filtered through a Chamberland filter; +, filtered but type of filter not stated.

(From Ref 4)

These last results had convinced many observers that all human warts, whatever their site or anatomic appearance were caused by the same virus (4). Immunologic data also seemed to show antigenic identify of viruses from mucosal, plantar, and ordinary warts (33). But further progress was blocked by the lack of an in-vitro system from which to harvest adequate amounts of virus (34,35,36). Only plantar warts seemed to contain usable amounts of virus. Laryngeal and genital ones had very little (37,38); thus investigators concentrated on investigating plantar wart virus and assumed that structural, biochemical, and physical properties of HPV from this source had general applicability (26,28).

Studies on the susceptibility of DNA from plantar wart virus to restriction enzymes seemed at first to confirm this genetic homogeneity, since several preparations from different pools of warts gave the same cleavage patterns (39,40,41). Only a modest degree of heterogeneity appeared in these studies. About 40% of molecules from plantar sources failed to display one cleavage site out of 13 such sites located on the physical map.

Figure 1



Physical map of the human plantar-wart virus (HPV-1) DNA.

(From Ref 41)

The one-virus theory seemed even stronger when viral DNA purified from multiple perianal warts of a single male homosexual subject was found to be indistinguishable from plantar material (23). Taking this theory still further, labelled cRNA made from plantar virus DNA was used to detect homologous DNA sequences in nuclei of anal warts in six of eight patients (23). Taken together with later findings, these studies make clear that the same or a closely related virus is found in plantar warts and at least some anal ones.

But anal warts of low virus content differed from genital warts in both epidemiologic (42) and immunologic studies (43,44). And other workers have failed to find sequences homologous to skin wart virus DNA in DNA extracted from condylomata and laryngeal papillomas (45,46).

While one preliminary study announced the finding of differences in capsid proteins of genital warts in comparison with plantar material (47) these studies depended mostly upon negative evidence.

The first positive identification of a second major type of HPV came from a French team (29) who isolated large numbers of virions from the many warts on the hands of a single severely affected patient (ML). The extracted DNA's of plantar HPV and MLHPV differed only slightly in weight ($5.23.10^6$ and $5.26.10^6$ Daltons respectively) but were shown to be quite different by analysis with restriction enzymes. Orth, et al. found no sequence homology between DNAs of the ML agent and pooled plantar virons using cRNA-DNA or DNA-DNA hybridization. Using both electrophoretic and immunologic techniques they found marked differences between both early and late polypeptides synthesized by the viruses from the two sources. These differences amounted to a greater distance between the two HPV strains than that observed between the SV40 and polyoma agents and clearly established MLHPV as a second HPV. Similar results from a group of German workers (48) suggest that minor differences exist between various isolates of HPV_1, but that discovery of the distinctly separate HPV_2 had been delayed because of its association with relatively nonproductive infections. The German group estimated that HPV_2 causes 20% of ordinary and plantar warts most of which exhibit low virus production, while HPV_1 or its minor variants cause 70% of such warts, predominantly those with high yields of virus.

Recent immunologic studies have found evidence for the existence of more than two types of HPV. The syndrome of epidermodysplasia verruciformis also provides sufficient affected tissue to allow isolation of virus (49). When this virus was passed to normal subjects it caused only flat warts, not other morphologic types (50). Taken together with the antigenic differences found with virus from EV patients, the clinical data suggests that a specific virus, different from HPV_1, or HPV_2, causes flat warts. If so the evidence summarized above then suggests the existence of at least four major types: HPV_1 and $_2$, a genital-laryngeal HPV, and a flat wart HPV. Besides these major types it seems evident that long-term growth in the tissues of a single individual allows emergence of minor variations of the major types (48,49).

IMMUNOLOGIC RESPONSE TO WARTS (51)

Only sketchy information is available on the level and class of antibodies to wart virus present in the general population. Most studies have involved small samples, and since the information regarding multiple HPV's is new, have not matched their subjects adequately for type of wart. Even in studies of groups suffering from a single type of wart, many investigators have not matched for the duration of infection or the time since infection ended. Nor has the degree of productivity (number of virus particles) of the lesions received attention as a determining factor in the

immune response (52,53). Limited serologic surveys suggest that almost everyone has been infected by age 20 (54,55), that viral antibodies are found in 10-50% of patients with active warts and 20-100% of those studied at the time their warts are regressing (55,56).

Cell-mediated immunity (CMI) may play a more important role in protection against and self-cure of warts than does humoral immunity. Indications of possible impairment of CMI has been noted in patients with extensive genital warts (11) as well as in immunosuppressed patients (57,58) and those with secondary cell-mediated immune deficiencies (59). These and other recent studies (60,61,62,63) suggest that impairment of CMI may be a key factor, but it may in some patients represent an effect of longstanding infection with heavy antigen loads rather than a cause.

TABLE IV

Incidence of Present Viral Wart Infections

	Incidence (%)	Incidence before treatment (%)	Mean number of warts
Control subjects	2.3		1
Multiple myeloma	0		
Hodgkin's disease	29.6	22	6
Malignant lymphoma	20.1	12	16
C.L.L.	17.6	8	16
Systemic malignancy	4.5		8
B.C.C.	6.2		1

(From Ref 59)

CASE 1

T.S., a 73 year old white woman, PMH #37-39-16, was referred for hospitalization because of progressive infection with vaccinia virus occurring on a background of lymphosarcoma.

She has been vaccinated in childhood without complications. Five years before entry she developed fever, malaise, and lymphadenopathy. Node biopsy and further evaluation at Methodist Hospital in Dallas yielded a diagnosis of lymphoblastic lymphosarcoma for which she received radiotherapy and several courses of nitrogen mustard given intravenously.

Two years before entry she saw a local dermatologist because of persistent and recurrent warts on the hands, present for 'a number of years'. These had recurred despite repeated attempts at removal by local cautery,

fulguration, use of chemical caustics, etc. About 15 separate warts ranging from 1 mm to 3 cm in diameter occupied the palmar and dorsal aspects of both hands.

During the period before entry she received treatment with podophyllin cantharidin, chemical caustics, cryosurgery, and ultimately a trial of superficial radiotherapy. Each time temporary successes gave way to massive recurrences.

Three weeks before entry she returned with large recurrent warts and urgently requested treatment. A single vial of vaccinia was diluted to 3 ml and 0.1 ml injected into each of four large warts. Eleven days before entry the treated areas became red and swollen, a process which spread to the affected left hand. One week before entry she developed apparent lymphangitis. The injected warts developed large blisters.

On admission she appeared comfortable despite erosions at the site of of each inoculation. Secondary vesicles and erosions had developed at the tip of the nose and on the left shoulder. Viral cultures subsequently grew vaccinia virus from each of these lesions.

During her stay the white blood cell count ranged from 4300 to 5800, normal differential, platelets 90,000 to 112,000. The serum protein electrophoresis showed decreased albumin and total globulin (2.6 and 0.23 grams % respectively).

For a diagnosis of progressive vaccinia in an immunosuppressed host her physicians administered Marboran 200 ml/kg initially followed by 50 ml/kg every six hours for three days. Vaccinia-immune globulin was also given. Beginning healing was noted within three days of completing Marboran. On the 19th hospital day she was discharged to convalesce uneventfully.

The best studies of immune phenomena during regression of warts involve measurements made both before and after the warts regress, so that each patient serves as his own control (53,61,64,65). These studies indicate that regression of warts is associated with both an increase in CMI (61,65) and specific humoral community (64,65) but neither the sequence of events nor the causal role of these changes has been clarified fully. It seems possible for instance that CMI directed against a wart-related cell surface antigen may disrupt infected cells, release large amounts of antigen, and stimulate a humoral outpouring. The actual mechanism may vary with the type of wart involved. Flat warts seem to resolve after development of cellular infiltration and inflammation, while these events are more subtle if they occur at all with resolution of ordinary warts. One Japanese report noted that ordinary warts persisted in one patient while inflammatory regression occurred in his flat warts (70), not a surprising observation if as we now suspect, antigenically separate viruses are involved. Whatever the cause, new warts may develop after regression of old ones in from one third to one half the patients (71,72).

One must mention non-immunologic causes for regression of warts. If immunologic mechanisms offered solid immunity the risk of recurrent warts should fall below that in controls, while in fact it is roughly three times higher (72). Any non-immune hypothesis must account for the fact that spontaneous, non-inflammatory regression overtakes two thirds of ordinary warts within two years of their inception (71). All standard treatments for warts except surgery or the non-standard treatment x-ray act to stimulate proliferation of affected cells. Some workers (72,73,74) have suggested that such stimulation hastens cure because: 1)either the virus-induced change in cellular proliferation is reversible (a process that has been described for polyoma [75]) or 2) that the single virus-transformed cell from which the wart was originally derived has reached the limit of its capacity for cell division (76,77).

TREATMENT (2,51,78)

TABLE V

The Treatment of Warts

PLANTAR WARTS	ORDINARY WARTS	MUCOSAL WARTS	PLANE WARTS
SALICYLIC ACID [PLASTER, COLLODION, (DUOFILM)	SALICYLIC ACID - COLLODION (5 or 10%)	PODOPHYLLIN	SUGGESTION OR BLAND LOTION
FORMALIN	CANTHARIDIN (NAILS)	5-FLUOROURACIL	CRYODESTRUCTION (VERY SUPERFICIAL)
CURETTAGE OR BLUNT DISSECTION	CRYODESTRUCTION	CRYODESTRUCTION	5-FLUOROURACIL
	CURETTAGE	DNCB	DNCB
	DNCB		

Why treat at all if warts are likely to regress on their own? While the routine treatment of every wart would be unnecessary for the patient and burdensome for the health care system, plantar warts can cause pain and ultimately disable the patient, periungual warts can readily become infected, and vulvo-vaginal warts are associated with the risk of laryngeal papillomatosis in the exposed newborn. For these reasons as well as cosmetic ones the decision may be made to treat. It should be recalled, however, that the best results (79) reported usually do not exceed a cure rate of 70%.

TABLE VI

Results of various treatments used in cases of single warts compared with all patients treated.

Treatment	Single Warts		All Cases	
	Patients	Cured (%)	Patients	Cured (%)
Ointment and Lotion...	56 (10)	46.4	644 (67)	50.6
Freezing	111 (12)	82.9	683 (74)	68.8
3% Formalin	—	—	2 (–)	50.0
Podophyllin	9 (8)	11.1	25 (15)	24.0
Diathermy + General Anaesthetic ...	13 (1)	76.9	141 (26)	65.2
Remaining Treatments	175 (21)	66.9	458 (78)	56.6
Total Treated ...	364 (52)	67.6	1953 (260)	59.1
No Treatment ...	11 (1)	90.9	53 (4)	86.8
Total	375 (53)	68.3	2006 (264)	59.8

(Figures in brackets are numbers of patients treated in whom the results are not known.)

(From Ref 79)

Physical Methods

Surgery and electrosurgery: Under local or regional anesthesia the surgical curet can scoop out a wart. Alternatively it can be dissected by a blunt instrument (80) along natural lines of clearage at sides and base. Excisional surgery can also be used, but scarring is inevitable and recurrences in the scar are frequent. Electrodessication or fulguration uses a very high frequency alternating current from a cold electrode to create heat in the tissue to be destroyed. (Caution! This high frequency current may disturb function of cardiac pacemakers.) This altered tissue can then be curretted away. Lasers (81) and ultrasound (82) have been used as well.

Cryosurgery in the form of solid CO_2 or liquid nitrogen can be applied either with a simple cotton applicator or with more sophisticated sprays or mechanized devices. Cryotherapy was introduced in order to try selectively to destroy the epidermal tissue without injuring the deeper layers in a way that could cause scarring. Unfortunately the unwary therapist may freeze and thrombose underlying vessels if he applies excessive cold or pressure. This may lead to the necrosis which he wished to avoid. The method also causes significant pain during thawing. It is usually too painful for use on the foot or on anogenital lesions.

Chemical Methods

Salicylic acid, an irritant and weak corrosive whose mode of action is still uncertain, is the single most useful chemical agent for warts. It has been incorporated into creams, ointments, collodion, adhesive tape and even gels in concentration of 5 to 40%. For plantar warts the usual recommendation consists of frequent paring, and the application of salicylic

acid in collodion or in an impregnated, cloth-backed plaster to the wart repeatedly, often over the course of weeks. This technique is generally quite safe and harmless as long as the patient defers therapy when irritation develops, but thoughtless persistence in the face of discomfort can lead to deep corrosive change and scarring.

Great care must be used with trichloracetic acid or any of its congeners. These potent caustics may be used effectively but are hazardous in inexperienced hands.

Formaldehyde and glutaraldehyde have been used at 5% aqueous concentrations as soaks, or as 10-20% ointment in the case of formaldehyde. Both produce local anhidrosis through an action on the sweat ducts, both lead to skin dryness, brittleness and cracking, but only glutaraldehyde stains the stratum corneum brown.

Cautharidin 0.5% is used as a blistering agent (mid-malpighian level) that can be applied in collodion:acetone 1:1, especially round the nails where other medications or treatments could scar. Unfortunately this treatment sometimes cures only to leave a ring of new warts in a circle round the site of the old one.

Podophyllin, an herbal extract with colchicine-like properties, is used widely for mucosal warts (84). At 5% to 20% in alcohol or tincture of benzoin it can be applied by a cotton applicator to moist warts, the surrounding tissue protected with zinc oxide ointment, then the whole washed off in four to six hours. Like all treatment for warts, this one must be repeated, usually at weekly intervals.

Podophyllin is useless for ordinary or plantar warts which it cannot penetrate, and should not be used in pregnant women where systemic absorption may cause cardiovascular collapse or fetal abnormalities. Caution is imperative in treating any case of very extensive, very vascular condylomata, because of the risk of systemic absorption.

5-Fluorouracil 1 to 5% has been used successfully for anogenital warts that resist podophyllin (10). Again, treatment must be prolonged.

Immunotherapy

Initial enthusiasm for levamisole has faded with a negative double-blind trial (84). The use of dinitrochlor (or fluor) benzene as a sensitizing application may eventually find a secure place in therapeutics (85,86). In a preliminary study even condylomata appeared to respond more consistently to DNCB than to 5-FU (87). Unfortunately this mode of therapy regularly produces localized itching, swelling, and redness, occasionally of severe degree. A generalized rash may develop in a few. The sites of sensitization and challenge may hyperpigment in darker individuals. Sensitized individuals may later react to other nitrobenzenes or to chloramphenicol (88,89). Overall the complication rate exceeded 24% in one series and the success rate reached 66% in 35 patients (86).

Advantages of the method include lack of pain, no risk of scarring, no need for injection of local anesthesia. But its continued application to the point of cure requires unusual motivation.

Local vaccinations with smallpox vaccine (90) or BCG (91) both difficult to obtain and beset by reactions (92,93) have been used to stimulate cellular immune responses nonspecifically. Several reports have appeared of excellent cure rates after injection of formalin-or heat-inactivated wart material, at least in the approximately 50% of patients who develop specific CMI and IgG antibody in response to the procedure (94,95).

Hypnosis and Suggestion

Since individual warts tend to resolve spontaneously, hypnotherapy as well as some of those mentioned above may give the appearance of effectiveness without the substance. Nevertheless convincing reports have been published in which the "cure" has purposefully been confined to warts on one side of the body (96,97). Skepticism continues in some quarters (98) but the possibility that warts may respond to suggestion cannot be excluded.

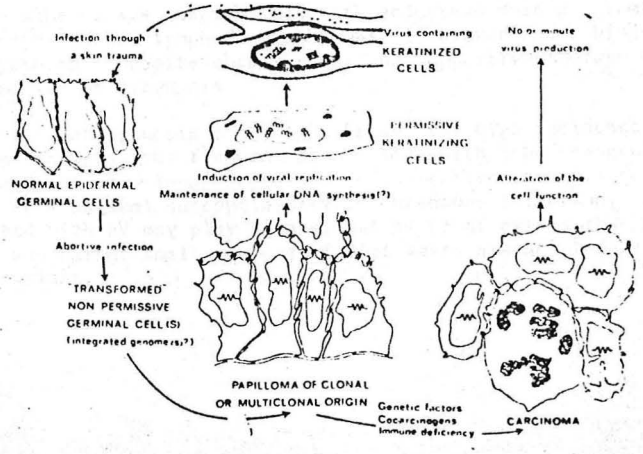
Can Wart Virus Cause Cancer?

The possibility of a role for HPV in human cancer has received little serious attention despite numerous circumstantial bits of information linking the two:

1) A related papovavirus, the Shope papilloma virus of rabbits, causes invading, destroying, and eventually metastasizing squamous cell carcinomata in up to 75% of experimentally infected domestic rabbits (99,100). Polyoma, SV40, and bovine fibropapilloma virus also display oncogenic properties in their own hosts.

Figure 2

Diagrammatic representation of a model for Shope papilloma virus interaction with cottontail rabbit epidermal cells.



(From Ref. 23)

2) Malignancies appear to develop occasionally within genital warts (20,101). These observations are rendered difficult to interpret by the postulate (22) that a low grade malignancy termed verrucous carcinoma may at first clinically resemble a condyloma but is nonetheless biologically malignant from the start.

3) In the rare familial disease epidermodysplasia verruciformis about 25% of patients eventually develop intraepidermal or invasive squamous cell carcinomas. In these lesions malignant conversion is accompanied by loss of demonstrable virus and occurs in a multifocal pattern mostly in sun-exposed areas (102,103). The additive effect of light, pointing to an enhancement of yield of tumors by co-carcinogens, is highly characteristic of the interaction of papilomaviruses with host tissues. Besides UV light, polycyclic hydrocarbons, and deficient immune function also increase the pathogenicity of such tumor viruses.

CASE 2 (104)

D.C., a six year old white male at first examination, CMC #129494, developed pink lichenoid papules on his face at age seven months. These spread to the legs and arms by one year of age and remained stable thereafter.

His psychomotor development was noticeably delayed. He suffered frequent upper respiratory infections and was hospitalized twice for pneumonia during the first two years of life. His parents were related to each other as first cousins but had two other normal sons and a normal daughter. No family members had flat warts.

The general physical examination was normal save for a mildly beak-shaped nose, shortened mandible, and high-arched palate. The thumbs and toes were normal as were the results of neurologic examination. Laboratory studies including urine amino acid screen, eeg, ivp, sweat-electrolytes, and lynphocyte karyotype were normal.

He had a positive delayed skin test to mumps antigen and was sensitized successfully to DNCB. The immunoglobulin levels and total lymphocyte count were normal.

At age nine he was hospitalized with abdominal pain and vomiting. Massive retroperitoneal lymphadenopathy was discovered and a biopsy showed Burkitt's lymphoma. Despite chemotherapy and supportive therapy he died within six months of diagnosis.

While the pathogenesis of EV is unknown, the high incidence of cosanguineous parents, the frequent association with other congenital anomalies, and the occasional appearance of defective immune function (9) all suggest some unusual susceptibility to cutaneous infection. The unique HPV associated with EV may play a role, but no proof exists that normal individuals who harbor small numbers of flat warts are not infected with the same viral variant.

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