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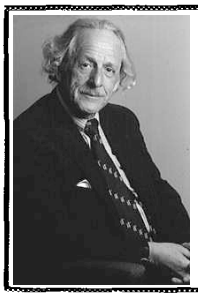

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All Sorts of Warts—Separating Fact from Fiction. Part 2. Treatment, Spontaneous Regression, and Key Publications

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Few diseases can claim as many "cures" as have been proposed for warts. In Part 2 of this essay, we describe conventional treatments (topical preparations; cryotherapy, or freezing; surgical removal; and so on), new promising therapies (interferon), and psychological treatment tactics (hypnosis and suggestion). We also highlight some of the more curious folk remedies for warts. Pertinent ISI® research fronts are identified and discussed. Theories of spontaneous regression, the unexplained disappearance of warts, are presented. Finally, a list of select journals that publish the key literature is provided.

Warts, those seemingly innocucus but annoying disfigurations that plague so many people, actually are not so innocent. Some benign warts undergo malignant transformation. As we noted in Part 1 of the essay,[1] warts are epithelial papillomas (a term used here and throughout wart literature synonymously with the word wart) caused by the human papillomavirus (HPV). So far, more than 50 different types of HPV have been discovered, and each one is responsible for distinct clinical manifestations.

In Part 1 we also discussed basic research fronts related to warts, traced their history, and identified the milestone works. In this second part we will focus on the treatments for warts—some based on scientific evidence and others on folk beliefs. We also will discuss the phenomenon of spontaneous regression and some of the theories as to why warts disappear by themselves. We will conclude the essay with a summary of journals that publish articles on warts.

Treatment

Throughout history there have been countless remedies—some magical, some conventional, some not so conventional—all believed to be "cures" for warts. Despite much effort, there is no single, specific, effective treatment for warts. Several therapeutic steps are usually necessary before treatment is successful.

F.E. Anderson, a physician in Tamsworth, Australia, thinks that warts probably can claim the highest number of folk remedies of all diseases.[2] Magical and botanical remedies have dominated most of the folk practices. Most cures for warts, however, are based on the notion of transferring the warts to another person, animal, or object, reports dermatologist Mary H. Bunney, Royal Infirmary, Edinburgh, UK. Sir Francis Bacon typified the thinking about warts during the sixteenth century. Ironically, considering his name, he rubbed his warts with pork fat, which he then hung in the sun to melt. By the time the pork melted, five weeks later, his warts had disappeared.[3] (p. 5)

In *The Adventures of Tom Sawyer*, Mark Twain wrote about using dead cats, spunk water (rainwater found in a tree trunk), and split beans rubbed with blood from warts to cure the malady.[4] Bunney[3] (p. 5) and J.C. Whorton,[5] Department of Biomedical His-

tory, University of Washington School of Medicine, Seattle, describe a number of popular folk practices. Warts were sometimes "sold" to a person who claimed to carry them away. During the nineteenth century, blood from warts was fed to animals. It was believed that the warts would transfer to the animals. Carollyn James, staff writer for *Science*, reports that ointments made from a variety of substances, including dandelion juice, castor oil, and onion juice, were concocted and rubbed on warts.[6] Other interesting remedies include rubbing warts with the blood of frogs or pigs or with new pennies, tying slugs to the lesions, and, oddly enough, secretly rubbing the warts on the father of an illegitimate child.[3] (p. 5),[5,6]

Modern research, too, has provided us with a number of options for treating warts. Before a specific treatment is started, however, a number of factors must be considered. The eventual outcome of treatment is influenced by the age of the patient, the kind and number of warts, and how long the warts have been present. In choosing a treatment for a particular patient, a physician must consider the possibility of spontaneous regression and weigh the discomfort and risks of a treatment against the patient's existing disability.[3] (p. 31) As Bernard Dixon, European editor of *THE SCIENTIST™*, points out, the spontaneous regression of warts within a short time is much more common in children than in adults. Physicians should take this into account when considering appropriate treatment, if any, for youngsters.[7]

Many warts can be treated at home by the patient with salicylic acid preparations and other topical medications. Bunney claims that these products can cure 70 to 80 percent of common warts and 80 to 90 percent of deep plantar warts.[8] However, because these agents are caustic, healthy skin must be protected when applying them.[7] Dermatologists Walter B. Shelley and E. Dorinda Shelley, Medical College of Ohio, Toledo, recommend soaking feet with plantar warts in a 4 percent formaldehyde solution. Children's plantar warts respond well to salicylic acid patches.[9]

Topical podophyllin (a mixture of resins from the stem and roots of the podophyllum plant) generally is used to treat plantar and genital warts. S.K. Tyring, Department of Dermatology, University of Alabama, Birmingham, and coworkers claim that the highest rates of cure are for small lesions found only on the external genitalia.[10] When physicians are treating genital warts in men and women with podophyllin, they should dust talcum powder over the treated warts so that the podophyllin does not smear onto normal skin.[9] Podophyllin should not be used by pregnant women because it is teratogenic. Others should be warned that there is evidence that podophyllin is carcinogenic.[3] (p. 44) Another topical agent, trichloroacetic acid, is used much like podophyllin and can be used if podophyllin fails.[9]

Cryotherapy, a technique in which warts are frozen, is the most popular and routine treatment used, according to Holger Kirchner, Institute of Virus Research, German Cancer Research Center, Heidelberg, Federal Republic of Germany.[11] Liquid nitrogen and carbon dioxide snow (dry ice) are the most frequently used freezing agents. As Brian J. Campbell, McKay-Dee Family Practice Residence Program, Ogden, Utah, notes, it is more effective to freeze and thaw warts several times rather than just once because there is greater cellular disruption with repeated freezing, resulting in wart tissue necrosis.[12] One drawback of cryotherapy is that it can be very painful. However, it is relatively safe and can be used on pregnant women.[8]

Surgical removal is another alternative therapy. Cutting of the wart directly is not recommended. Rather, curettage or cauterization is advised. Unfortunately, surgical procedures cause unnecessary scarring, and recurrence of the warts is high.[3] (p. 56) Carbon dioxide laser therapy is an alternative to surgical incision. It produces less scarring but is considerably more expensive.[12]

Dinitrochlorobenzene (DNCB) sensitization and challenge offer another treatment option. DNCB is a powerful skin sensitizer that causes a cutaneous hypersensitivity reaction that leads to wart destruction. Possible complications involved with this choice of therapy include unwanted sensitization of the person administering DNCB and cross-reactivity with industrial and agricultural chemicals.[12]

Chemotherapeutic agents (for example, methotrexate, bleomycin, and 5-fluorouracil) also are possible wart treatments. Bleomycin (manufactured as Blenoxane by Bristol-Myers Oncology Division, Syracuse, New York) is an antibiotic with antiviral and antitumor activity. Small doses of bleomycin sulfate are injected into resistant warts and are very successful. No systemic side effects have yet been reported with this procedure.[8]

Interferon seems promising in wart treatment. P.K. Weck and coworkers, Department of Immunology and Oncology, Burroughs Wellcome Co., Research Triangle Park, North Carolina, describe interferon as a natural substance produced by many cells when a viral infection is present. At low concentrations, interferon is nontoxic to cells and nonspecifically inhibits intracellular replication of viruses. When interferon is injected directly into warts, the warts progressively disappear.[13] Like other wart treatments, interferon may destroy abnormal cells. But it is unique in that it also eradicates HPV.[10] Philip Kirby, Harborview Medical Center, Seattle, adds that, although it cannot be explained, responses among female subjects given interferon for warts have consistently been better than responses among males.[14]

When administered systemically to epidermodysplasia verruciformis patients, interferon causes regression of warts and reduces HPV in tissues.[14] Interferon also has been used successfully and safely in the treatment of genital warts. Alvin E. Friedman-Kien, New York University Medical Center, New York, and coworkers report that interferon injections are effective in treating genital warts in patients who previously had been treated unsuccessfully, as well as in patients who had no prior treatment. Patients usually tolerate the injections well and there is no scarring.[15]

Studies involving the use of interferon in treating genital HPV infections have investigated administering the agent topically, intralesionally, and systemically.[14] Intralesional injections into the base of the warts have been found to be more effective than topical applications and less toxic than the systemic route.[15]

In addition to the many areas of basic research identified through the ISI® database, one small front explicitly related to the topic of wart treatment was identified. While there are many research fronts on interferon, one deals specifically with warts. Research front #86-3496, "Bleomycin, interferon, and other treatments of viral warts," involves 2 core and 11 citing articles. One[16] of the two core articles was written in 1976 by Bunney, mentioned earlier, and colleagues. S.M. Shumer and E.J. O'Keefe, Department of Dermatology, University of North Carolina School of Medicine, Chapel Hill, wrote the other core article.[17]

Psychotherapy

In addition to the above-mentioned procedures, psychological techniques—suggestions and hypnosis—have also been claimed to be effective. These techniques generally are used when the other treatments discussed earlier have failed. Adding to their appeal is that they offer a painless, noninvasive type of cure.

In their book *Clinical Hypnosis: Principles and Applications*, Harold B. Crasilneck and James A. Hall, University of Texas Health Science Center, Southwestern Medical School, Dallas, offer an explanation for the apparent success of hypnosis in eradicating warts in some cases. They suggest that there may be a direct physiological connection between the brain and the skin. Both

are derived from ectodermal embryonic tissue.[18] Crasilneck's work involving hypnosis and the treatment of dermatological disorders was cited in a recent essay on hypnosis.[19]

Other explanations for the success of psychological methods in treating warts include alterations in the blood supply, skin pH, and temperature or a stimulation of antibody production.[3] (p. 81) The more plausible of these explanations is the theory that hypnosis alters the velocity of the capillary blood flow to the warts.

Critics of hypnotherapy contend that spontaneous regression is actually responsible for the disappearance of the warts. However, A.H.C. Sinclair-Gieben, University of Aberdeen, and D. Chalmers, Aberdeen Royal Infirmary, UK, reported the findings of their study of patients with warts on both sides of their bodies who had been treated by hypnosis for the warts on one side. The warts on the other side were not treated and served as controls. After 5 to 15 weeks of hypnotherapy, the warts on the treated side disappeared. The control warts were still present.[20] However, Walter B. Shelley notes that although everyone is interested in hypnotherapy in regard to warts, it is an area that has never fulfilled its promise. Shelley does not refer his patients for hypnotherapy because its cure rate is very low.[21]

Brian A.P. Morris, a physician in Ontario, Canada, explains that most hypnotherapists use the direct-suggestion method while the patient is in a trance.[22] The hypnotherapist makes hypnotic suggestions such as "These warts are going to leave," or "These warts will be gone very shortly" to the patient during repeated visits until the desired result—the disappearance of the warts—is obtained.[18] Morris, however, believes that the "mental imagery" method is much more effective. Patients visualize their immune systems actually attacking the warts (the Simonton visualization technique). He proposes that hypnosis evokes an immune response that results in the eventual disappearance of warts.[22]

Candace Pert, National Institute of Mental Health, Bethesda, Maryland, cites warts as an "example of how a viral disease has a psychosomatic component."[23] Previously, I have discussed the mind-body link between the immune and the nervous systems and how the two systems can interact to cause disease or promote good health, a field known as psychoneuroimmunology.[24] Pert believes that the wart story is "psychoneuroimmunology in action."[23]

Warts Across Cultures

While advances in research have provided modern treatment techniques, some cultures continue to adhere to less technical methods. In some parts of the UK, cow manure is still rubbed on warts. And, in 1974, a wart charmer appeared on a BBC television program and shared some of his wart incantations.[3] (p. 5) All such methods may, in fact, simply involve the power of suggestion.

Not surprisingly, the Chinese use acupuncture. However, moxibustion, where heat from a moxa stick or incense heats warts, is also used. (A moxa stick is made from soft, combustible material such as leaves, cotton, or wool bound together.) Gregory S. Chen, Acupuncture Clinic, Birmingham, Alabama, explains that these two procedures work because they activate and sensitize the immune system, which then destroys the papillomavirus and cures the warts. Moxibustion is more effective than acupuncture because the localized heat not only improves circulation and stimulates the immune system but also deactivates the virus. The method is very safe and economical. Like hypnotherapy, it has cured warts that did not respond to more conventional therapies. Patients, both adults and children, can be taught to treat themselves successfully.[25]

Spontaneous Regression

While many warts are resistant to treatment—to both sophisticated and primitive

Table 1: Selected list of journals that publish articles on warts. A = title, first year of publication, editor, and publisher. B = 1986 impact factor. C = number of articles on warts or papillomavirus covered between 1984 and 1987 in *SCISEARCH®*. D = total number of articles in each journal covered in *SCISEARCH* between 1984 and 1987.

A	B	C	D
Acta Dermato-Venereologica (1920) N. Thyresson, ed. Almqvist & Wiksell Periodical Stockholm, Sweden	0.71	8	688
Archives of Dermatological Research (1869) E. Christophers, ed. Springer-Verlag Heidelberg, Federal Republic of Germany	1.14	15	934
Archives of Dermatology (1920) K.A. Arndt, ed. American Medical Association Chicago, IL	1.78	20	1,515
EMBO Journal (1982) M. Birnstiel, ed. IRL Press Oxford, United Kingdom	8.14	17	2,070
Genitourinary Medicine (1925) A. McMillan, ed. British Medical Association London, United Kingdom	1.10	12	306
International Journal of Cancer (1966) N. Odartchenko, ed. Alan R. Liss New York, NY	3.53	17	976
International Journal of Gynecological Pathology (1982) S.G. Silverberg, ed. Raven Press New York, NY	1.37	10	196
Journal of General Virology (1967) C.R. Pringle, ed. Society for General Microbiology Reading, United Kingdom	2.33	21	1,281
Journal of Investigative Dermatology (1938) D.A. Norris, ed. Elsevier Science Publishing New York, NY	3.74	25	3,519
Journal of Oral Pathology (1972) H.M. Fullmer, ed. Munksgaard International Publishers Copenhagen, Denmark	1.12	15	533
Journal of the American Academy of Dermatology (1979) J.G. Smith, ed. C.V. Mosby St. Louis, MO	1.84	15	2,135
Journal of Virology (1967) A.J. Levine, ed. American Society for Microbiology Washington, DC	4.43	55	2,313
Obstetrics and Gynecology (1952) R.M. Pitkin, ed. Elsevier Science Publishing New York, NY	1.54	21	1,883
Virology (1955) W.K. Joklik, ed. Academic Press Duluth, MN	3.31	25	1,489

methods—many warts disappear by themselves. Skin warts (common, plane, flat, and plantar) are the most likely to undergo spontaneous regression. Laryngeal papillomas and condyloma acuminata also regress by themselves. Deep plantar warts found on the bottom of the feet often begin to hurt and turn black right before they fall out. Common warts and plane warts occasionally itch before they regress, but they generally just shrink and disappear.[3] (p. 23)

Most skin warts eventually disappear by themselves. Spontaneous regression generally starts between three months and five years after they appear and is complete in three to four weeks. Bunney estimates that 20 percent of normal patients will lose their warts spontaneously within three months of their initial appearance.[8] She believes that regression is influenced by the type and amount of HPV and the patient's immunologic state.

The exact mechanism of spontaneous regression is still not known. Both cell-mediated immunity (immunity controlled by T lymphocytes) and humoral immunity (mediated by antibodies produced by B lymphocytes) appear to play key roles in wart regression. As Kirchner reports, the wart antibodies IgG and IgM are strongly linked to all regressing warts.[11] IgG antibodies appear to be more strongly linked to regres-

sion than IgM antibodies. Also, Warwick L. Morison, St. Helier Hospital, Surrey, UK, one of the core authors in research front #86-7565, "Papillomavirus in renal allograft recipients," noticed an increased response in cell-mediated immunity to viral antigens when warts were ready to regress.[26] And, although there is no absolute evidence, in some instances the disappearance of the warts may be the result of nothing more than a set life span of the wart cells.

In their experiments, Keiji Iwatsuki, Department of Dermatology, Hamamatsu University School of Medicine, Japan, and colleagues found that in plane wart regression the regression is a systemic reaction, with a noticeable infiltration of mononuclear cells into the upper dermis and epidermis. This supports theories that spontaneous wart regression is influenced by cell-mediated immunity.[27] Mitchell E. Bender, Department of Dermatology, University of Minnesota Medical School, Minneapolis, explains that the mononuclear cells in regressing warts attack the epidermal cells infected with HPV with tumor-specific surface antigens. T lymphocytes were found to be the predominant attacking cells, and, with the help of activated macrophages, they destroy wart tissue.[28]

Whatever the mechanism of spontaneous regression, it should be taken into consideration when treatment options are being reviewed so that unnecessary pain and expense for the patient can be avoided if regression seems to be likely. A perhaps more important observation concerns the insularity of medical specialties in general. It has been my perception, and it certainly is not unique, that specialists seem never to talk to members of other specialties. For example, I could not find any papers reporting combined wart therapy involving both hypnotherapy and cryotherapy or chemotherapy. In fact, one dermatologist did not question the potential value of psychological techniques, yet he would not recommend it to his own patients—even to those who had been treated without much success for several years.

Relevant Journals

Table 1 provides a selected list of journals that publish articles on warts. A preliminary journal list was compiled by using keywords, concepts, and prominent authors in online and manual literature searches. The core and citing papers of the relevant research fronts were scrutinized. Journal titles that appeared frequently were added to the list, which eventually was carefully condensed. The list of journals covers most areas of wart research, but it is significant that treatment by hypnosis is not reported in these journals.

A search of the *SCISEARCH®* database shows that, between 1984 and 1987, there were 1,000 articles published on warts or papillomavirus. Not surprisingly, most of the literature in this field turns up in virology and dermatology journals. Considering warts' potential for malignant conversion, it is surprising that only one cancer journal is mentioned.

Concluding Remarks

This concludes our essay on warts. While many treatment options are available, a real cure for warts has yet to be discovered. Even though warts are rarely fatal, I wonder if they attract adequate attention in the biomedical research communities throughout the world. Nevertheless, we should applaud the progress that has been achieved through basic research in the past decade.

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