
The Cervical Dilemma

*Some warts may
be better left untreated*

By KATHY A. FACKELMANN

Susan's annual visit to the gynecologist reveals a nasty shock: Her routine "Pap" smear suggests she has been infected with a sexually transmitted papillomavirus. With no symptoms, Susan is at a loss to date when she might have picked up the bug, or from whom. She's already angry about the news when the doctor delivers the real kicker — a warning that the infection increases her risk of developing a deadly form of cancer.

Susan's doctor suggests she might want to consider undergoing laser surgery to destroy the "flat warts" caused by the virus. These subtle thickenings, invisible to the naked eye, may eventually progress to cervical cancer, a disease that kills 4,500 U.S. women annually.

So Susan agrees to the surgery. Why take a chance?

But a new study suggests Susan and her gynecologist may have made the wrong decision. Very preliminary findings hint that laser treatment of the flat warts may actually speed their progression to dysplasia, a precancerous condition characterized by abnormally proliferating cells. In fact, the controversial findings suggest that for women who exhibit the earliest signs of human papillomavirus (HPV) infection, the best prescription may be no treatment at all.

Microbiologists have identified more than 50 different types of HPV. These viruses cause a variety of skin growths — from harmless plantar warts to cauliflower-like genital-tract protrusions. However, only five types of HPV, particularly HPV-16 and HPV-18, are associated with cervical cancer. By some estimates, 15 percent of the sexually active population carries sexually transmitted HPV, which can lurk in cells without producing outward signs of infection.

Because epidemiologists have linked these viruses to cervical cancer, gynecologists now advocate aggressive treatment — including laser surgery — for dysplasia. But some recommend an all-out attack much earlier, before HPV-infected women show symptoms other than the microscopic flat warts. In such cases, they advocate killing the infected cells with a powerful laser or with cryotherapy, which uses a chilled metal

probe to freeze the warty epithelial cells that line the cervix.

But women subjected to these invasive treatments fare no better than women who get no treatment at all for their HPV-associated flat warts, report Karyn Grimm Herndon and her co-workers at Northwestern University Medical School in Chicago. In fact, their data indicate that flat warts are more likely to progress to dysplasia in women treated with laser surgery than in those receiving no treatment. Herndon presented the findings last month in New Orleans at the annual meeting of the American College of Obstetricians and Gynecologists.

"The results are surprising," says co-author David Scott Miller. Prior to the study, both he and Herndon relied on laser therapy to treat women with HPV-induced cervical flat warts. Now, both advise against laser surgery or cryotherapy in these cases.

The Chicago researchers didn't set out to pan their own prescription for flat warts. Although their retrospective study arose from an observation that laser treatment sometimes failed to prevent dysplasia, Miller says he never dreamed the data would suggest that this treatment might actually foster dysplasia.

To compare the outcomes of different treatments, the researchers reexamined the medical charts of 128 women aged 14 to 60. An inserted, microscope-like device called a colposcope had unmasked HPV-associated cervical flat warts in each patient — and no sign of dysplasia. The researchers found that one of five physicians had determined the course of each woman's follow-up based on professional preference and not on the severity of the patient's HPV infection. The result was that 28 patients had no treatment, just observation; 57 received cryotherapy; 36 underwent laser surgery; and 7 received some other treatment, such as surgical removal of the uterus.

The good news, Herndon says, is that regardless of treatment, the majority of women in each category showed no evidence of HPV infection more than one year after the initial diagnosis. Indeed, three out of four women in the observation-only group lost their flat warts — a finding that suggests the body's immune system can drive the virus into a dormant state, Herndon says.

Now for the bad news: The Northwestern researchers discovered that women whose warts were treated with laser surgery faced roughly twice the risk of developing precancerous tissue, compared with women in any other group. For example, 11 of the laser-treated women (31 percent) developed cervical dysplasia, compared with five of the women (18 percent) in the observation-only group

and six assigned to cryotherapy (11 percent). The differences between the observation and cryotherapy groups were not significant, the team notes.

Even more alarming, the study hinted that flat warts progressed to dysplasia more quickly in the laser-treated patients than in the other groups. From those data, the team estimates that only 57 percent of women receiving laser surgery would remain free of dysplasia for two years, compared with roughly 82 percent of the women in the observation group and 89 percent of the cryotherapy group.

Though no malignancies were diagnosed during the study, Herndon cautions that all of the women remain at risk of flare-ups of the HPV infection.

The mechanism underlying the laser's poor performance remains a mystery. However, scientists know that after laser treatment, epithelial cells left untouched by the destructive beam proliferate rap-

idly to heal the injured cervix. Miller speculates that such cells somehow are more vulnerable to infection by any remaining HPV.

Although this "interesting and provocative" study failed to control for all the factors that could affect its conclusions, the findings raise some important questions that will require further investigation, observes Douglas W. Laube of the University of Iowa College of Medicine in Iowa City.

Other scientists warn against jumping to conclusions on the basis of one preliminary investigation. "There are 100 potential holes in this paper," says HPV expert Ralph M. Richart of Columbia University College of Physicians and Surgeons in New York City. He charges that the study's small size and the fact that the patients

were randomly assigned to treatment groups represent potentially fatal flaws. Richart recommends that women with HPV-induced flat warts continue to seek treatment, even laser surgery. (Until recently, Richart relied on laser surgery to treat cervical flat warts. Now he removes the HPV-infected growths with a newer mechanical loop.)

To address the criticism of colleagues like Richart, the Northwestern researchers plan a follow-up trial in which they will randomly assign women to various therapies and then track the outcomes.

Until then, Herndon believes the latest data strongly argue for a decidedly low-tech—and low-cost—approach to managing cervical flat warts. The cost of regular office visits to observe the status of the infection compares quite favorably, she notes, to the \$1,000 price tag for laser surgery. □

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adaptations" added to a characteristic anatomical pattern among Neandertal infants and children, he says. If firmly identified, this pattern might provide a critical guidepost for evaluating juvenile skulls in the Israel caves.

Fragmentary skulls of Neandertal children, the youngest of whom died between 1 and 2 years of age, show that their heads were considerably larger than those of modern children, according to Smith and Michael Green of the University of Tennessee in Knoxville. They theorize that the accelerated growth of the Neandertal's head and body started in the womb,

representing an adaptation that minimized heat loss among vulnerable newborns entering the refrigerated world of ice age Europe. Indeed, modern populations inhabiting cold regions feature markedly greater birthweights than their counterparts elsewhere, the researchers note.

Smith and Green propose that the expansion of cartilage at the skull base may have kicked off prenatal growth acceleration, exerting considerable pressure on cranial bones and creating the relatively flat cranial bases of Neandertal adults. Cranial base flattening may also have set in motion other growth patterns—such as a projecting lower face—that

emerged more clearly after childhood.

"We need to examine developmental patterns of Neandertals," says Nancy Minugh-Purvis of the Medical College of Pennsylvania in Philadelphia. "For now, I take a wait-and-see attitude toward the question of Neandertals in the Middle East."

New evidence suggests that an evolutionary continuum from Neandertals to modern humans may indeed have operated in eastern Europe, Minugh-Purvis says. Her assertion stems from a study of a partial cranium found in a Yugoslavian rock shelter. She and Jakov Radovic of the Croatian Natural History Museum in Yugoslavia carefully pieced together fragments of the approximately 35,000-year-old specimen, which came from a child about 6 years old. Some of the fragments came from excavations conducted more than 80 years ago; others had turned up within the past decade.

Sediments at the Yugoslavian site dating to about 80,000 years ago have yielded unmistakable classic Neandertals, but Minugh-Purvis thinks this partial cranium represents a transitional hominid bridging Neandertals and modern *H. sapiens* from the same area. She notes, for instance, that the angle and size of the specimen's brain case and its moderate brow ridge fall squarely between measurements of the same traits in the two established groups.

While controversy persists over Neandertal contributions to modern human origins in eastern Europe, the evolutionary situation in western Europe remains even murkier, she adds.

"From Europe to the Middle East to Asia, there are still enormous gaps in our knowledge about Neandertal fossils," says Mann.

Like a recurrent dream, Neandertals continue to excite the imagination while retaining their mystery. □

Asian gene lines show antiquity

Fossils no longer monopolize the search for human origins. In 1987, a scientific team headed by Rebecca Cann of the University of Hawaii reported that, compared with people in other parts of the world, Africans show significantly more mutations in their mitochondrial DNA—genes inherited only from the mother. The researchers argued that these mutations accumulate at a relatively constant rate over time; their assertion led to the controversial conclusion that modern humans originated in Africa about 200,000 years ago and then spread throughout the world, developing racial differences in the process. Reports on mitochondrial DNA denied Neandertals any substantial genetic contribution to modern human evolution.

The latest mitochondrial data still support an "out of Africa" model, but Asian genetic lineages appear surprisingly old, says Rick H. Ward of the University of Utah in Salt Lake City.

Ward has examined a particularly fast-evolving segment of mitochondrial DNA obtained from 180 Indians belonging to tribes in the western United States, as well as the same mitochondrial segment obtained by other researchers from Japanese and Papua New Guineans. All three populations may have left Asia within the past 50,000 years, he says.

Assuming a relatively conservative DNA mutation rate, Ward finds that the three mitochondrial lineages originated between approximately 110,000 and 140,000 years ago. Considerable genetic diversity apparently accumulated in each lineage prior to migration out of Asia, he adds.

Overall, however, modern humans exhibit far more genetic similarities than differences, Ward points out. "Genetic changes over the last 50,000 years have been small compared with human cultural changes," he maintains.

— B. Bower