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CONTAGION

A sometimes lethal sexual epidemic that condoms can't stop

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Last year, I was called by a friend in California, Dan West, about his daughter Jennifer, a junior at a small college in western Massachusetts. Jenny had had an abnormal Pap smear on a routine examination she was given at the student health service. The doctor found an irregular growth in her cervix which, he said, might be cancerous. It was the result of a sexually transmitted virus called papilloma. “She was stunned and frightened, and so am I,” Dan said. “We’d feel more comfortable if she could be seen in Boston.”

Having arranged for Jenny to visit a gynecologist at the Boston hospital where I practice, I met with her ahead of time. (Names and identifying details have been changed for confidentiality.) A young woman with short, curly black hair and dark eyes, Jenny said she had had no symptoms of an infection—no fever, pelvic discomfort, or vaginal discharge. After a long pause, she told me she had informed the college doctor that she had had intercourse with only two partners in her life, and never without a condom. She added that the doctor had met her statement with a skeptical look. “I didn’t like his attitude,” Jenny said. “He made me feel as if I must be promiscuous.”

At our hospital, Jenny underwent a colposcopy—a procedure in which the gynecologist uses a magnifying instrument to examine the tissues of the vagina and the cervix. The area was painted with diluted acetic acid, a vinegarlike solution that causes papilloma-infected tissue to turn snowy white. Just inside the opening of the cervix, the lesion was now clearly visible—a ragged plateau of whitened tissue. After numbing the area with a local anesthetic, the gynecologist used an electric cautery to burn a border around the growth, and removed it.

Later that week, I sat with the pathologist who was analyzing the excised lesion. The lining of the cervix normally consists of orderly layers of tightly packed cells: under the microscope, it resembles a landscaped stone wall, with a graduation of large, nearly cubical cells at the base and thin, closely joined cells at the top. Jenny’s tissue, though, looked as if it had been blown apart by a cannon, the finely ordered architecture having been replaced by a palisade of bloated cells with bizarre, coal-black nuclei. “Severe dysplasia,” the pathologist concluded, pointing out the characteristic ballooned look of the papilloma-infected cells. “But it hasn’t yet progressed to carcinoma.” DNA analysis of the tissue revealed that Jenny had type 16 papilloma virus—the virulent genital strain that most often leads to cervical cancer.

The classical medical teaching was that cervical cancer is a disease of ‘bad girls,’” says Dr. Joel Palefsky, a professor at the University of California at San Francisco and a leading expert on human papilloma viruses. In fact, however, papilloma virus is the most common sexually transmitted infection in the United States and Europe, occurring at some point in up to seventy-five per cent of sexually active women. Nor have safe-sex practices stopped the infection rate from growing dramatically over the past couple of decades. “Unlike other sexually transmitted pathogens, like gonorrhea or H.I.V., papilloma virus is easy to pass around,” says Palefsky, who has been outspoken in calling for an aggressive response to this epidemic. “The doctor asks a young woman with an abnormal Pap smear or a worrisome lesion ‘Have you had unsafe sex?’ and by that he means intercourse without a condom.” Where papilloma is concerned, intercourse can be unsafe even with a condom. That’s because the papilloma virus lives in cells of the outer skin as well as in the interior cells lining the vagina, cervix, anus, and urethra. Condoms do not cover the entire shaft of the penis and do not block contact with pubic skin. So, during the petting and frottage of foreplay, or during intercourse with a condom, papilloma-laden skin cells from Jenny’s boyfriend could have come in contact with her vulva and vagina, enabling the virus to track up to her cervix. In addition, the minor friction of frottage and intercourse is believed to cause microscopic abrasions that make it easier for the virus to enter the vagina and the cervix. Even dead skin cells can contain the papilloma virus and remain infectious for days.

It has been estimated that about ten million American women—most of them in their late teens and twenties—have active infections. A million of them have diseased, and perhaps precancerous, tissue as a result. About eighty thousand have early cervical cancer that is still contained within the inner lining of the tissue. Some sixteen thousand have cancer that has invaded the cervix more deeply, and each year about five thousand of those will die. In Africa and Asia, and on the Indian subcontinent, where women don’t have regular Pap tests, cervical cancer from papilloma is the most common cause of cancer-related death.

Widespread though papilloma is, few people even know when they’re infected, since it seldom produces noticeable symptoms. The Centers for Disease Control have no program for tracking the virus. Indeed, until recently there were no sensitive methods for detecting it. Papilloma virus cannot be cultured in the laboratory from clinical specimens, so in the past doctors had to make a diagnosis by examining cells obtained by Pap smear. But Pap tests are notoriously inaccurate: any exam will miss between twenty and forty per cent of infected women. Now that DNA testing for papilloma is available, studies have begun to collect more accurate information about the incidence and the course of infection. One such study published last year followed more than six hundred female students at Rutgers who were examined every six months. The results were instructive: in the course of thirty-six months, new papilloma infections occurred in more than forty per cent of the young women. Most infections lasted about eight months and then subsided, but after two years about ten per cent of the students still carried the active virus in the vagina and the cervix. And those persistent infections were most common with the virulent, cancer-linked types of the virus.

Papilloma is a relatively small virus—essentially, two strings of DNA enclosed within a spherical protein shell. Viewed under an electron microscope, it looks something like a golf ball. There are as many as a hundred papilloma types, and they can infect virtually any cell on the skin or on the inner lining of tissues. For unknown reasons, certain types of the papilloma virus target the skin of the hands and feet, others the lining of the mouth, and still others the genitalia.

These viruses were first recognized as causing warts on the hands and feet—areas of hypertrophied skin filled with keratin, the hard protein that forms toenails and fingernails. Warts used to be considered mainly a cosmetic nuisance rather than a forerunner of life-threatening cancers, and the types of papilloma that cause warts on the fingers and toes are, indeed, largely innocuous. Viral strains that target the face can make skin cancer more likely, though. (Oddly, these types of papilloma virus are most heavily shed from the eyebrows.) Still other strains, which grow primarily in the lining of the mouth, result in elevated, pea-size nodules that can develop into aggressive and fatal squamous cancers. A link between genital papilloma infections and cervical cancer was first demonstrated in the early eighties, by Harold zur Hausen, a German virologist. Since then, scientists have identified about twenty papilloma types that primarily infect the cervix, vulva, vagina, penis, and anus. Of these, four are most often found within the malignant cells of genital cancers, with type 16 accounting for about half of the cases in the United States and Europe. We also know that papilloma is implicated in ninety-five per cent of cervical-cancer cases.

In fact, cervical cancer is probably the best understood example of how viral infection can lead to malignancies. Cell division is regulated largely by two proteins—one called Rb and the other known as p53. Dr. Peter Howley, working first at the National Cancer Institute and now at Harvard Medical School, found that two genes in the papilloma virus, E6 and E7, make proteins that attach themselves to p53 and Rb, respectively, and deactivate them, causing the cell to reproduce without constraint. “It’s a progressive process,” Howley says. “The virus is the initiating event. First, it causes the cell to grow wildly. As it does so, it accumulates more and more damaged DNA that cannot be repaired, thereby accumulating mutations that turn it into a cancer cell.”

Those silent molecular changes are reflected in the cellular changes that the pathologist had pointed out on Jenny West’s Pap smear. At an early stage, there are subtle distortions in the size and shape of the cells as the virus causes them to expand. Then their neat, uniform arrangement along the cervical lining is destroyed as the damaged cells grow in a haphazard fashion. Full-blown cancer occurs when the cells start to ignore normal tissue boundaries and threaten to invade more deeply into the muscle of the cervix and the uterus.

The important thing, of course, is to catch it early, and if lesions can be detected and removed before they turn malignant, cervical cancer can often be prevented. The primary method of detection is still the Pap test, named for the pathologist George Papanicolaou, who pioneered the method in New York in the nineteen-twenties. The Pap test has since become a routine part of the gynecological exam. First, a speculum—an instrument that

opens to expand the vagina—allows the doctor to examine the cervix directly. Then a spatula is inserted into the expanded vagina until it meets the lower cusp of the cervix, where it is rotated, so as to scrape off several layers of cells. Carefully withdrawing the spatula, the doctor deposits a viscous sample of cells and mucus on a glass slide. Next, a cotton-tipped swab or brush is inserted deep into the canal of the cervix that leads to the uterus. The area where the cervix merges into the uterus is known as the transformation zone, and it is there that precancerous lesions and cervical cancers most frequently develop. The cotton swab retrieves a second sample of cells, which is spread on another glass slide.

The procedure is crude and inexact. If the cells are not spread on the slides in an even and uniform manner, they can clump and prevent accurate inspection. Sometimes other contents of the cervix, such as blood, bacteria, or yeast, contaminate the sample and prevent the detection of abnormal cells. If the cervical cells are exposed to air too long before being fixed on the slides, they can be distorted. But the greatest threat to accuracy is human error. The average slide contains anywhere from fifty thousand to three hundred thousand cells. Some technicians and pathologists joke that it's like "Where's Waldo?" But with Waldo, the character has consistent features, and you know he's around somewhere. With a Pap smear, someone has to inspect every cell on the slide: if the sample includes only a few abnormal cells in a dense background of healthy ones, they can easily be missed, particularly by overworked readers. These problems led to the establishment of national guidelines eleven years ago, and since then technicians have been forbidden to read more than a hundred slides a day. Some experts think that number is still too high, and, indeed, studies have shown that technicians are most accurate in their assessments at the beginning of their shift, with their acuity waning significantly over time. To make things worse, government inspectors have found widespread violations when they visit Pap-testing centers.

Even when a cytology laboratory is well run, though, Pap remains a poor screening test. What compensates for its error rate is the frequency with which it is administered. The progression to cancer generally takes place over a period of between ten and twenty years, so having a regular Pap test—once a year is the standard practice—improves the chance that any pathology will eventually be detected. Unfortunately, some lesions become cancerous quite swiftly—sometimes within a year or two. In fact, fifty per cent of all women who have developed cervical cancer have had a Pap test within five years of the diagnosis. And at the meeting of the Society of Gynecologic Oncologists held in San Francisco this spring a great deal of attention was paid to the need to improve early-detection techniques. The Food and Drug Administration has approved a new method, called ThinPrep Pap Test, which is designed to get around many of the technical problems of preparing the Pap slides. Rather than being deposited on glass slides by hand, the cell samples from the spatula and the cotton swab are suspended in a liquid solution. A machine then filters out the cells from the suspension and deposits them automatically in a thin layer on the glass slides. This uniform monolayer is easier for a technician to inspect, and the process removes contaminants like mucus, bacteria, and yeast. Though the ThinPrep method improves the detection of precancerous lesions, it is estimated to add fifteen to twenty-five dollars to the cost of a standard Pap test (which is usually around fifteen dollars), and that's a concern for some H.M.O.s. The F.D.A. has also approved two new devices—papnet and the AutoPap Primary Screening System, in

which computers display potentially abnormal cells for review and analysis by pathologists. There has been some dispute about how much accuracy is gained through the use of these automated systems, and, as with ThinPrep, some insurers have balked at the additional expense (usually between three and ten dollars).

One way to improve on Pap diagnosis is to test directly for the papilloma virus. Many physicians believe that combining the Pap test with direct virus testing may prove particularly useful when a Pap test comes back with its most common indeterminate result, called ASCUS—atypical squamous cells of undetermined significance. “That is a namby-pamby diagnosis, because in some women it indicates real pathology and in others it’s meaningless,” Palefsky says. DNA testing for papilloma isn’t yet widely available but may become so in the next few years; several companies have developed kits that will tell doctors when carcinogenic strains are present. From five to ten per cent of ASCUS readings—and there are two million such readings a year—are later found to indicate precancerous or cancerous lesions.

That proved to be the case with Mira Allen, a high-school teacher I cared for several years ago. She had few risk factors for cervical cancer—only one sexual partner prior to her husband—and she had had a regular Pap test. The first sign of an abnormality was an ASCUS reading when she was thirty years old. Mira and her husband, who were well educated and eager to begin a family, were worried by the indeterminate reading. But the doctor’s advice was to wait another six months before repeating the test, since many benign conditions cause atypical cells, and even if the test did signal an early lesion it was likely to be a slow-growing one. The second Pap test was no longer equivocal: the slide revealed the signature bloated cells with large coal-black nuclei. So the gynecologist performed a colposcopy, and within the lip of Mira’s cervix he found a shiny area with a mosaic surface that resembled ivory tiles. A biopsy showed deeply invasive cervical cancer. She underwent surgery, in which the cervix, the uterus, and the adjoining lymph nodes were removed, and then had radiation therapy to destroy any remaining cancer cells. Mira suffered the frequent complications resulting from the treatment—diarrhea and inflammation of the bladder—but for three years there was hope that the treatment had worked. Then she developed lower-back pain. X-rays showed a metastasis to the spine; a CAT scan revealed lesions in her liver. Radiation therapy was given to alleviate the lower-back pain by shrinking the tumor around her spinal cord, and Mira was referred to me for chemotherapy.

Mira’s husband sat tensely at her side as she recounted her social and medical history in a soft voice. Because both she and her husband had read about the disease, and knew that the old medical textbooks linked it to multiple sex partners and a history of other venereal diseases, the couple watched my face for signs of disdain. But she was hardly the stereotype of the old medical textbooks. All it would have taken was one partner who carried a carcinogenic strain of papilloma virus, such as type 16.

I treated Mira with high doses of combination chemotherapy, but the drugs checked the advancing cancer only temporarily. Within a few months, the tumor had spread to her lungs. At the age of thirty-four, Mira Allen died, the victim of a carcinogenic papilloma virus.

But what about her husband? Was he at risk, or putting others at risk? At the time, these thoughts hadn't crossed my mind. "Doctors ignore the male," Palefsky says. "When we see someone with syphilis or gonorrhea, we always test the partner. But a man with, say, human papilloma virus 16 or 18, each strongly associated with cervical cancer, can walk around and infect other women without knowing it." The Centers for Disease Control do not recommend testing the sexual partners of a woman with the papilloma virus, on the ground that the partners will already be infected and that there is no cure. In Palefsky's clinic, though, he and his colleagues make a point of seeking out the male partners of infected women. When appropriate, they'll perform a colposcopic examination of the penis: as with cervical colposcopy, the surfaces around and within the urethra are painted with a vinegarlike solution and the distinctive lesions are biopsied. Palefsky acknowledges that this is not standard practice. But, he argues, papilloma virus in men is associated with precancerous lesions of the penis and can progress, albeit at a very low frequency, to penile cancer. "People say don't bother, because the majority of infections are ultimately combatted by the immune system," Palefsky told me. "But such a man, when still infected, is a public-health risk to other women, and what if we can prevent this, as well as his own penile cancer, through early detection?"

These concerns arise with gay men, too. The epithelium of the anus and the anal canal is similar to that of the vagina and cervix, with a transformation zone at the junction between outer squamous cells and internal glandular cells. Among sexually active urban gay men, about sixty per cent of those who are H.I.V.-negative carry the papilloma virus in the anal area; nearly ninety-five per cent who are H.I.V.-positive have the papilloma virus. Gay men have been found to carry the same range of genital papilloma viruses—including the cancer-associated types 16 and 18—that women do. And sexually active gay men often carry many different papilloma-virus types. "In the anus," Palefsky says, "it's papilloma-virus soup."

Extrapolating from a recent study in San Francisco, researchers estimate that thirty-five out of every hundred thousand H.I.V.-negative gay men have anal cancer. This is about the same rate of cervical cancer that was found in women before they began to receive routine Pap tests. (Among H.I.V.-positive men, Palefsky estimates the rate to be twice as high.) "If I were a general practitioner for gay men, I would do an anal Pap test on all my patients," Palefsky told me. Anal cancer resulting from the papilloma virus is also a risk for women who engage in anal intercourse or in frottage with their buttocks. These women, Palefsky believes, also need to receive regular anal Pap testing. Having pioneered this technique in San Francisco, he is now training physicians around the nation to perform anal Pap tests.

The most effective way to protect against the papilloma virus and prevent anal and genital cancers would, of course, be a vaccine. Individuals would need to be immunized before becoming sexually active. The benefits of such a vaccine would be particularly significant in the developing world, where women's health services are minimal. But designing one will be difficult. People's immune response appears to be specific to the type of papilloma virus, so that a person protected against, say, type 16 would still be susceptible to other strains associated with genital cancer, such as 18. Recent data

suggest that there are also subtypes or variants within type 16, and perhaps within other types as well. Moreover, the types of papilloma virus associated with cervical cancer vary by geographic area. Types 39 and 59 are most prevalent in Central and South America. Type 45 is common in West Africa. With the increase in travel and emigration, these carcinogenic strains will probably start to emerge in the United States and Europe. So a vaccine with a cocktail of several types would have to be created. Still, two companies, MedImmune and Merck, have begun early-phase studies on the safety of vaccinating women against cancer-linked genital papilloma viruses. There are also attempts to develop a so-called therapeutic vaccine, which would boost the immune system of someone who was already infected. Such vaccines would target the E6 and E7 proteins, those viral proteins that sabotage cell-growth regulation.

Jennifer West is being followed closely with Pap tests and a colposcopy every four months. After her diagnosis, she informed her boyfriend of her infection. He was both dismayed and more than a little defensive. He had never heard of the papilloma virus, and protested that he had no symptoms of a venereal disease. Jenny explained that she hadn't, either, and that the virus could have passed between them despite their use of condoms. Cells from his urethra tested positive for type 16, but there were no discernible lesions, and nothing to excise. "All that the two of us can do is wait, and hope it will pass," Jenny said. Many experts now believe that, as with herpes, once you are infected with papilloma, you are infected for life. There is no treatment. In many cases, an active infection is controlled by the immune system and becomes dormant. No one can predict whether, or when, the virus will become active again.