Medicine by John Grauerholz, M.D.

New screening test for cancer

Within a year, the test promises to increase the yield of useful information for one of the commonest forms of cancer in women.

A new weapon is about to be added to the armamentarium of cancer detection. Within the next few months to a year, testing for Human papillomavirus (HPV) in Pap smears and cervical biopsies will be commercially available. This holds the promise of substantially increasing the yield of useful information from the widely-used screening test for one of the most common forms of cancer in women.

HPV is a DNA virus which infects surface tissues such as the skin and the lining of the genital tract. Among the 56 varieties of HPV are the viruses which cause plantar warts on the soles of the feet, the common skin wart, as well as warts in such diverse locations as the larynx and the genital tract.

Among these different types of papillomavirus, two in particular, types 16 and 18, are associated with 60% of invasive cancers of the uterine cervix, that portion of the uterus which forms the end of the female vagina, and from which the majority of cancers of the uterus have their origin.

Two other types, 6 and 11, are found in genital warts and other benign growths of the genital tract in men and women.

HPV was implicated in cancer of the cervix in an article published in the Aug. 2, 1986 issue of the British medical journal, *Lancet*. In a study of 100 women with early precancerous changes of the cervix, HPV type 16 was identified in 85% of those who progressed to more severe precancerous changes.

The authors stated that "the detection of HPV 16 appears to identify women at high risk of rapid progression to advanced CIN [precancerous changes—ed.] and possibly cancer."

The development of the Pap smear, named after the Greek physician, George Papanicolaou, was instrumental in reducing the death rate for cancer of the cervix, once one of the leading causes of cancer deaths among women. By detecting early, precancerous changes in cells shed into the vagina, physicians were able to remove the affected areas before the development of invasive cancer.

This led to a 70% decline in the death rate for cervical cancer over the last 40 years.

Recently, however, there has been a tripling of the death rate for cervical cancer among women under 35 years of age. Many authorities believe that the increasing sexual activity which has characterized the last two decades is responsible for the sharp increase of benign and malignant disease of the cervix. For example, a West German study of cervical smears from 9,295 women found that precancerous changes and HPV infection were most common in those between the ages of 20 and 30 years, and that 65% of visits to physicians for genital warts are made by patients 15 to 29 years old.

As a result, there has been growing concern about false negative Pap smears, especially since there has been a recent increase in the number of questionable Pap smear findings. Thus, in some cases, the Pap smear may fail to reveal cancer or precancerous lesions, allowing a potentially curable tumor to become incurable by the time it is detected.

The addition of HPV testing to the Pap smear would constitute a "double-barreled" approach to this problem. By identifying lesions of the cervix which contained one of the cancer-associated types of HPV, patients with these lesions could be followed at more frequent intervals or have the lesions removed directly.

Until recently, such extensive testing for HPV has been hindered by the difficulty in detecting the virus. Microscopic changes in the tissue are suggestive of infection, but not diagnostic, and the virus refuses to grow in culture. Virus particles in tissue taken directly from warts can only be seen under the electron microscope after a careful preparation procedure. However, in most lesions of the cervix no virus particles can be found.

In these cases, detection of virus DNA is the only way to establish the presence of the virus. Until recently this was done by a lengthy and complicated procedure, known as the Southern blot assay. While this assay has a near-100% ability to reveal the presence of HIV, its technical demands have limited it to laboratories with the necessary time and personnel.

A number of rapid, simple, commercial assays are now being developed to overcome this problem. Most of these assays are based on the use of DNA or RNA probes which specifically bind to virus DNA. The probe is coupled to either a radioactive compound, an enzyme, or a dye. After treatment with the labeled probe, the specimen is examined for the presence of the bound label.

At present the Food and Drug Administration has limited all these assays to research use until their value and accuracy have been field-tested and more is known about the link of HPV to cervical cancer.