

The lifesaver with an image problem

THE THOUGHT OF A PAP SMEAR IS ENOUGH TO BRING A LOOK OF EXTREME DISTASTE TO MANY WOMEN'S FACES, BUT THIS VITAL TEST HAS CONTRIBUTED GREATLY TO REDUCING DEATHS FROM CERVICAL CANCER. LISA MITCHELL PUTS IT UNDER THE MICROSCOPE.

PHOTOGRAPHER: PAUL JONES

Dr George Papanicolaou, or "Pap" as he was affectionately known, would probably have been peeved to learn that the Pap smear test he introduced in the late 1920s to detect cervical cancer is so disliked by women around the world. You could just about hear the groans all over Melbourne two years ago after 30,000 letters went out to patients for a Pap smear test recall (a local pathology company had problems meeting the required quality assurance program requirements).

Although the procedure is simple and quick, having a Pap smear taken is viewed by many women as invasive and embarrassing. The bottom line, however, is that the test is highly effective at saving lives. Australia's National Cervical Cancer Screening Program started in 1991 and the Government estimates nearly 70 per cent of women are now screened, although older women still tend to avoid the dreaded "internal". Evidence suggests that having Pap smears every two years can prevent up to 90 per cent of squamous cell cervical cancer, the most common form of cervical cancer. Even so, about 800 new cases are diagnosed each year in Australia and about 250 women will die from the disease.

There is considerable room for human error in Pap smear testing and abnormalities can go undetected. Regular testing is highly important in order to allow early detection and reduce the risk of missing serious problems. To begin, the GP inserts a speculum into the vagina in order to see the cervix clearly. The doctor then scrapes the cervix and smears the sample, which usually contains about 300,000 cells, onto a glass slide that is sent to a laboratory for testing.

It doesn't take much to contaminate that sample: blood or mucus on the slide can make it tough to see the cells; air drying might affect the sample's quality; the cells need to be properly preserved using an alcohol fixative; and they must be scraped from an area of the cervix called the "transformation zone" to provide the best sample.

The transformation zone is the area between the squamous and glandular cells where abnormalities most often occur, says Dr Annabelle Farnsworth, president of the Australian Society of Cytology and director of cytopathology (a branch of anatomical pathology) at Douglass Hanly Moir Pathology in Sydney.

"The cervix has two types of cells. The squamous cells that, like your skin,

provide protection and hold everything together, and the endocervical, or glandular, cells that make the mucous that is important to the fertility cycle . . . The cervix is a very active area hormonally, and in the transformation zone, the cells are in constant flux." But the T zone is not always accessible or easy to find. For example, in postmenopausal women the zone tends to retreat higher into the cervical canal.

"Pap smear analysis is a demanding job," says Dr Farnsworth. "A scientist will analyse between 40 to 50 slides a day. You need an enormous amount of discipline to sit still all that time and you need to be a bit obsessive about your work."

Screeners must have a scientific background. It takes about two years to complete basic training before they can sit an exam set by the Australian Society of Cytology (the study of the function, structure and pathology of cells) and begin their search for abnormal cells. Should a screener find an abnormality, the smear will be sent to a pathologist for final diagnosis.

"The cell looks a bit like a fried egg with its round nucleus and surrounding cytoplasm that holds everything together,"



Dr Annabelle Farnsworth

“There are very grey zones when you are trying to distinguish between levels of abnormality.”

says Dr Farnsworth. “When abnormality occurs, the nucleus becomes very enlarged and it can start to look like a cauliflower, which indicates there are changes going on inside it. Normal cells have 46 chromosomes, but once you start getting cancerous cells, you might have 138 chromosomes. We can’t actually see them, but the distortion of the nucleus suggests they are multiplying.”

With about 300,000 cells per sample, colour-coded staining helps to highlight any suspicious patches. The scientist applies three stains to the slide: blue to highlight the nucleus and red and green to highlight the cytoplasm. A normal nucleus will appear even-coloured throughout, while an abnormal one will look spotty or pool in clumps of colour, says Dr Farnsworth.

“With minor lesions, the colour difference in the nucleus and the infolding and irregularity of the nucleus will be less.

One of the problems with cytology is that it is still a very subjective test, and there are very grey zones when you are trying to distinguish between levels of abnormality.”

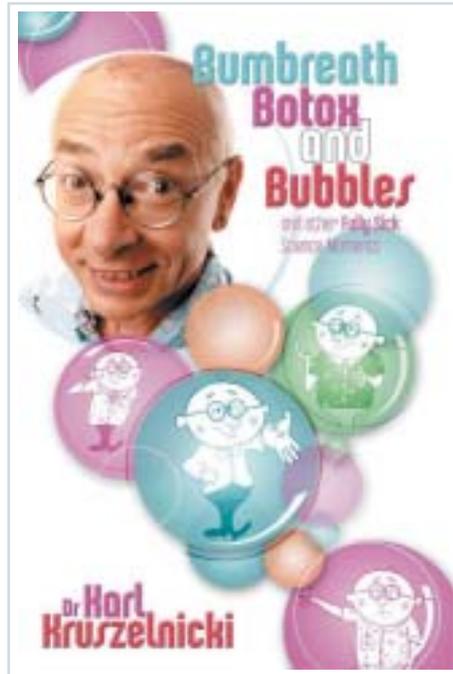
Pap smear results return six levels of abnormality. The first, minor atypia, indicates very slight changes detected in the cells that could be due to inflammation or infection. One such infection is the wart virus, or Human Papilloma Virus (HPV), of which there are 150 sub-types. Thirteen of these are at the heart of almost all cervical cancers, says Dr Farnsworth. “There are other compounding factors that cause cancer of the cervix, but you will not have the disease without some type of wart virus present. HPV is very common.”

The next three levels of abnormality are CIN1 (Cervical Intraepithelial Neoplasia), which is a low-grade abnormality, and CIN2 and CIN3, which are high-grade abnormalities that indicate cells are growing in a manner that could

develop into cancer. These low and high-level abnormalities are mostly found in sexually active women aged between 25 and 35. In Dr Farnsworth’s laboratory, which tests about 200,000 Pap smears each year, about 4 to 5 per cent of samples return minor atypia or CIN1 results, while one in 1000 shows CIN2 or CIN3 results.

For atypical results, doctors usually recommend having more frequent Pap smears and giving the cells a chance to heal themselves, but the detection of wart virus and CIN1, CIN2 and CIN3 currently warrants deeper investigation by colposcopy and biopsy. The guidelines for action on CIN1 results are under review by the National Health and Medical Research Council, however, and may be downgraded to more regular Pap smear testing. This is a very controversial review with the recommended change in the Guidelines in relation to the management

Thanks to George Papanicolaou and his wonderful wife, Andromache, millions of women today are being saved from cancer of the cervix. And it all started with George smearing vaginal cells onto a glass slide....



Mrs Pap Smear by Dr Karl Kruszelnicki

Today, the second most common form of cancer that kills women in Western society is cancer of the cervix (breast cancer is number one). But thanks to the famous Pap smear, we can detect cancer of the cervix before it digs in locally and/or spreads throughout the body, and successfully treat it. The Pap smear is named after Dr George Papanicolaou, who did a Pap smear on his wife virtually every day for 20 years.

Who collected Mrs P's Pap smear?

In the early days George was rather discreet about his daily Pap smear from his wife. In fact, he and Andromache kept quite a few details deliberately vague. Later on, George would introduce her as 'my wife and victim'.

George wrote some 150 scientific papers, and received many honorary degrees and awards. His portrait appeared on postage stamps of the USA, Greece and Cyprus, and the 10,000 drachma Greek note.

Mrs Papanicolaou, who was the intellectual equal of her husband as well as a willing volunteer, was eventually recognised as late as 1969. The American Cancer Society gave her a special award and declared her 'A Companion In Greatness'. I personally reckon she deserves more.

Dr Papanicolaou died in 1962 and his wife, Andromache, died in 1982. Dr Charles Cameron said of Dr Papanicolaou: 'He was a giver of life: he is in company of the great: he is one of the elective men of Earth who stand for all eternity like solitary towers along the way to human betterment. We are deeply in his debt.'

We are especially deeply in debt to his wife, Andromache, who had a Pap smear every day for 20 years. In her case, once a day did not keep the doctor away.

'Mrs Pap Smear' extract from Bumbreath, Botox and Bubbles by Dr Karl Kruszelnicki. Bumbreath, Botox and Bubbles is published by HarperCollins Publishers.

for low grade lesions not supported by the Royal College of Pathologists of Australasia.

The next step in clarifying those grey areas left by cytology is histology, or the analysis of tissue structure from a biopsy. Enter the colposcope, a magnifying instrument used to view the cervix through a speculum inserted into the woman's vagina. A gynaecologist takes a biopsy, or four-millimetre pinch of cervical tissue, that is sent to the laboratory for analysis, says Dr Farnsworth.

"We slice it very thinly, place it on a glass slide and stain it to make it easier to read . . . It is like looking at a topographical map; those extra features help you to delineate the grey zones between levels of abnormality."

The newest development for pathologists in Pap smear technology is the liquid-based cytology test, she says. As yet, the method has not been approved for Medicare rebates, but manufacturers of liquid based technology claim it will wipe out any margin for error and that a single smear test will allow GPs to test for several conditions simultaneously, including various sexually transmitted diseases. It is like having a second opinion, says Dr Farnsworth, but it does mean a duplication of the Pap smear test and analysis.

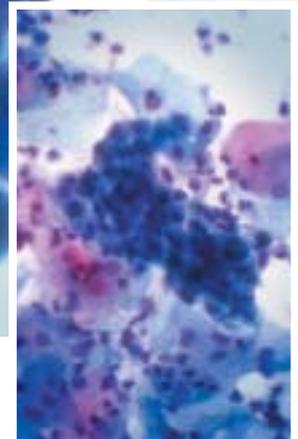
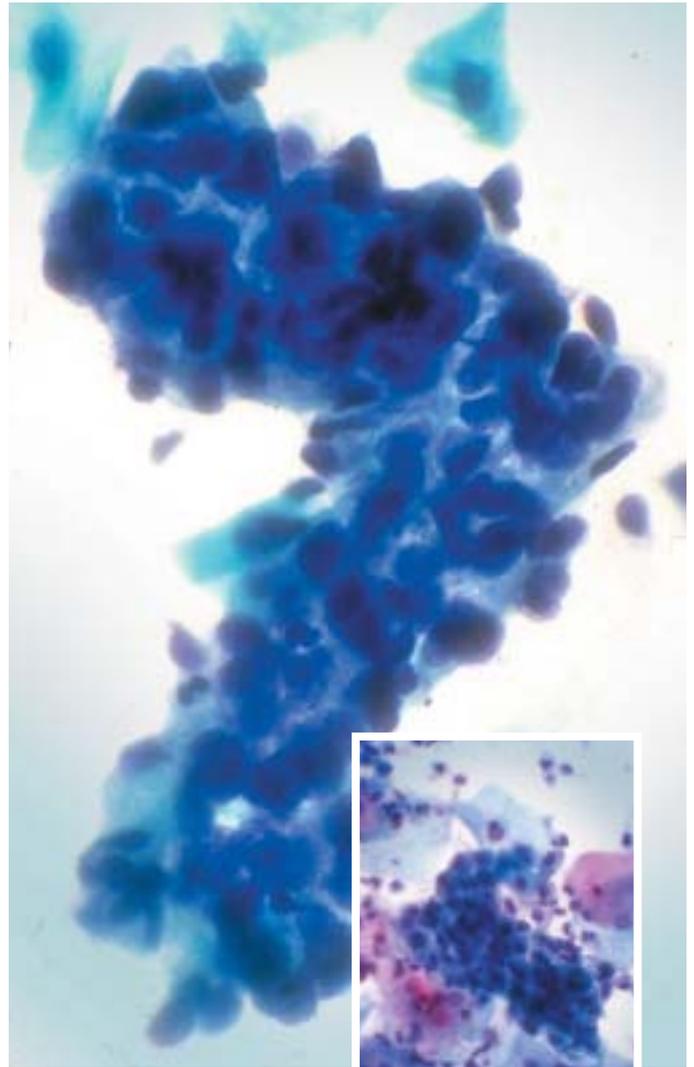
"Liquid-based cytology is available in Australia but women have to pay \$35 extra for it. It is taken at the same time as the Pap smear but instead of smearing the cells onto a slide, GPs rinse the smear-taking instrument into a vial of fluid and send the vial to the laboratory. There is much less chance of contaminating the sample."

Australian pathology laboratories are also investigating a new computerised device to read liquid base samples that could speed up the testing process and cut back the current two-week turnaround of tests to a few days, Dr Farnsworth says.

"You still need a scientist to do the analysis, but the machine scans the slide for the 22 most abnormal cell patches and then directs the slide to those exact areas. The scientist doesn't have to laboriously inspect the 300,000 cells from end to end. It's a huge labour-saving device that could revolutionise Pap smear testing." 🔥



Above: Lining up in the lab :
Scientist check smear tests for abnormal cells.
Right: Images from the microscope



DIAGNOSIS

A Pap smear involves having a speculum inserted into the vagina so the doctor can view the cervix clearly. The doctor scrapes the cervix for a cell sample that is sent to a pathology laboratory for cytology (cell) analysis. There are six possible levels of result.

- Normal.
- Minor Atypia, refers to minor changes in the cells.
- Human Papilloma Virus, or wart virus, in the cells of the vagina and/or the cervix. HPV is one of several known factors that cause cervical cancer. Colposcopy examination and biopsy analysis recommended, however guidelines for HPV action are under review.
- Mild dysplasia, or CIN1, a low-grade cell abnormality that is not cancer and that may heal itself or become worse. Colposcopy examination and biopsy analysis recommended, however guidelines for CIN1 action are under review.
- Moderate dysplasia, or CIN2, a high-grade abnormality that indicates cells growing in an unhealthy way. It is usually eight to 10 years before cancer may develop. Colposcopy examination and biopsy analysis recommended.
- Severe dysplasia, carcinoma or CIN3, a high-grade abnormality that can mean cancerous cells or cells in high danger of becoming cancerous. Colposcopy examination and biopsy analysis recommended.

TREATMENT

- Laser destroys abnormal cells using the heat from a laser beam.
- Diathermy destroys abnormal cells using a high-frequency current that generates heat.
- Cryosurgery destroys cells by freezing them.
- A wire-loop excision scoops the cells from the cervix with a wire loop.
- A cone biopsy entails minor surgery that removes a cone-shaped section of the cervix.

PREVENTION

- After a normal result, return for a Pap smear in two years.
- After an atypical result, return for Pap smears every 12 months until obtaining a normal result.
- After an HPV result, and possible treatment, return for a Pap smear every six months until you have two normal results.
- After a CIN1 result, and possible treatment, return for a Pap smear every six months for the first year, then every two years after that (guidelines for acting on CIN1 results are under review).
- After a CIN2 or CIN3 result, and possible treatment, return for a Pap smear every six months for one year, then yearly for the rest of your life.
- All women who have ever been sexually active are advised to have a Pap smear every two years. Registering with the National Cervical Cancer Screening Program through a GP will ensure patients are notified for check-ups.
- Women who have had hysterectomies but still have part of their cervix intact will need to have regular Pap smears.

Source: <http://www.cervicalscreen.health.gov.au>