WORKSHOP PROCEEDINGS

ISSUES IN CERVICAL CANCER SCREENING: Seeking Alternatives to Cytology

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MARCH 2-4, 1994

JHPIEGO Corporation

ACKNOWLEDGEMENTS

We would like to thank the participants at the Cervical Cancer Screening Workshop for their input into the working meeting and their assistance in compiling these proceedings.

Financial support for this publication was provided by JHPIEGO Cooperative Agreement DPE-3045-A-00-7004-00 with the Agency for International Development. The views expressed in this manual are those of the authors and do not necessarily reflect those of USAID.

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ABBREVIATIONS

CIN	Cervical intraepithelial neloplasia
CIS	Carcinoma in situ
DHLY	Discounted healthy life years
FP	Family planning
GP	General practitioner
GTI	Genital tract infection
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HUEH	Haitian State University Hospital
ICC	Invasive cancers of the cervix
IEC	Information, Education, Communications
JHPIEGO	Johns Hopkins Program for International Education in Reproductive Health
LEEP	Loop electrosurgical excision procedure
LMP	Last menstrual period
LOCIS	Low-power optical cervical screening
MEAC	Maternidade Escola Assis Chateaubriand
MOPH	Ministry of Public Health
Pap Smear	Papanicolau smear
PATH	Program for Appropriate Technology in Health
PVN	Predictive value negative
PVP	Predictive value positive
SIL	Squamous intraepithelial lesions
STD	Sexually transmitted disease
TBA	Traditional birth attendant
YKB	Yayasan Kusuma Buana
YKI	Indonesian Cancer Foundation
WHO	World Health Organization

BACKGROUND

1. Preface

From March 2 to March 4, 1994, the Johns Hopkins Program for International Education in Reproductive Health (JHPIEGO) hosted a workshop to review the status of cervical cancer screening worldwide and to discuss alternative methods of detecting cervical cancer. The specific objectives of the workshop were to:

- Provide background information on cervical screening methods
- Review the current status of cervical cancer screening in developing countries
- Discuss issues related to the accuracy of Papanicolau smears (Pap smears)
- Discuss alternatives to Pap smears for cervical cancer screening
- Review issues to consider in evaluating alternatives to Pap smears for cervical cancer screening

Thirteen persons participated in the workshop including four international experts from the Latin America and the Caribbean, Africa and Asia regions, five guests speakers from other interested international and national organizations involved in this reproductive health issue, and three JHPIEGO staff members. A full list of participants is provided in **Appendix I**.

The workshop included both presentations and group discussion. The presentations were designed to update participants on the current status of cancer screening and treatment approaches in the host country of the participants, and to provide state-of-the-art information on cervical cancer based upon the experiences of our US-based guests. A detailed agenda is summarized in **Appendix II**.

Group discussion was oriented toward assessing the feasibility of using alternative screening methods for the early detection of cervical cancer and its precursors. There was consensus that given the acknowledged problems of resources, facilities and trained personnel that such an assessment would be of value to women in the developing world. The group then focused its discussion toward designing a study to test the sensitivity and specificity of visual screening of the cervix as compared to cytology (Pap smears). It is anticipated that the results of this workshop, in particular, the consensus gained on study design issues, will provide the basis for a project aimed at testing the instrinsic qualities of an alternative cancer screening approach and ultimately improving access to reproductive health services.◆

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2. Overview of Cervical Cancer and Cervical Cancer Screening in Developing Countries

Vivien Davis Tsu, PhD

Cervical cancer is the most common cancer in the developing world and the leading cause of cancer death among women in developing countries. The limited data available suggest that, worldwide, there are at least 450,000 new cases of cervical cancer each year, of which almost 80% occur in the developing world. Given the long course of illness and the fact that women in developing countries seldom seek early treatment, the data suggest a pool of over two million women with invasive cervical cancer exists. According to global World Health Organization (WHO) estimates, 300,000 women die from cervical cancer every year, mostly in poorer countries (1994). This results in a tremendous loss to families and, subsequently, to nations themselves. In addition, the health care system is burdened by many patients who are terminally ill with a disease that is almost entirely preventable.

There are considerable differences in incidence rates between and within regions. The striking difference in incidence rates between developed and developing countries is attributed primarily to the differential access to effective screening programs aimed at detecting and treating pre-cancerous conditions: 40-50% of women in developed countries have been screened for cervical dysplasia in the past five years, as compared with only 5% of women in developing countries (WHO, 1986). Wide variations within regions also are apparent and are probably due to different distributions of key risk factors. The highest rates are seen in parts of Asia, tropical South America, the Caribbean, and East and Middle Africa (Meheus, 1992). A zone of low risk stretches from Pakistan to Egypt, with low to moderate rates in Europe and North America (Parkin, 1991).

Despite the differences in overall rates, the age distribution is similar throughout the world, with a rise that starts in the early 20s, continues up sharply in the 30s, and plateaus at 40 to 50 years of age (Parkin, 1991). This distribution has been the basis for WHO recommendations to concentrate screening efforts on women 35 and older. A few case series and studies from cancer registries in certain African countries have reported more than 20% of cervical cancer cases among women under 35, but the vast majority of cervical cancer is found among older women.

We do not have more recent information to suggest what the epidemiological impact of the human immunodeficiency virus (HIV) epidemic may be, but there are several studies that support the idea that HIV-positive women are at increased risk for cervical cancer (Judson, 1992). In areas where infection with HIV-2 is common, the risk of invasive cancer may be particularly high, since HIV-2 is associated with a significantly longer period of immunosuppression than is HIV-1. As populations age, we also can expect to see increased rates of cervical cancer. The global epidemic of sexually transmitted diseases (STDs) suggests conditions that will promote an increasing incidence of cervical cancer. Even with the scanty data available, it is evident that cervical cancer is a significant problem and likely to get worse.

Accumulated data from several decades of research strongly support the view that the primary causal agent of cervical cancer is genital infection with human papillomavirus (HPV). Commonly accepted risk factors for cervical cancer (including history of STDs and history of multiple sexual partners or a partner with multiple partners) are probably proxy indicators of HPV exposure. Sexual behavior and other risk factors such as high or early parity are hard to address in a preventive strategy. Since there is no vaccine for HPV yet and condoms do not

appear to provide much protection, screening to detect pre-cancerous lesions is the chief preventive strategy.

Because cervical cancer develops slowly and has a detectable and treatable precursor condition, it can be prevented by screening and treating at-risk women. Aggressive screening and follow-up can reduce mortality by more than 70%, and data now indicate that most mild-to-moderate dysplasias regress to normal spontaneously (Kiviat et al., 1992). Therefore, current thinking supports a clinical strategy aimed at detecting and treating severe dysplasia/carcinoma in situ (CIS) and monitoring mild and moderate dysplasia. Data from eight developed countries indicate that the cumulative rate of invasive cervical cancer could be reduced by about 84% by screening women aged 35 to 64 every five years, and 64% by screening every 10 years (WHO, 1986).

In a 1993 paper produced by the Program for Appropriate Technology in Health (PATH) for the World Bank called "Cervical Cancer in Developing Countries: A Situation Analysis," cervical cancer control efforts in 25 developing countries were reviewed. The review revealed that screening efforts have had only limited success for a number of reasons including:

- Limited screening services
- Failure of programs to target or reach at-risk women and limit frequency of screening
- Inadequate laboratory services, trained personnel, and Pap smear supplies
- Difficulty in client follow-up
- Inadequate follow-up diagnostic and treatment services
- High cost of services
- Limited awareness of cervical cancer as a health problem
- Cultural obstacles to providing services

What appears to be needed are programs aimed at raising women's awareness of this serious sexual behavior-related problem coupled with simple, inexpensive methods to diagnose and treat early cervical lesions (dysplasia/CIS) before they become invasive.

Proper clinical follow-up of women with abnormal cervical findings is critical to program success. Further research is needed into treatment options appropriate to developing world settings. Destructive methods such as cryotherapy and excisional methods such as diathermy loop excision of the transformation zone are of particular interest, given their relative low cost and simplicity. While cryotherapy is effective and requires only a small capital cost, it is associated with profuse watery discharge and possible infection afterwards and requires resupply of CO_2. Loop excision is more expensive, is more often associated with bleeding, and requires electricity and anesthesia, but may be more effective with larger lesions.

While cytology has been the standard recommended approach to screening, other strategies are being considered in order to address some of the constraints to screening listed above. Unaided visual inspection during a speculum exam for early cancer detection, referred to as "downstaging" by WHO, has been evaluated in India and was considered effective in identifying women with cancer at an earlier, more treatable stage (Singh et al., 1992). Adding acetic acid to the cervix, which turns suspect lesions white, improves the sensitivity of visual inspection. Visual inspection aided by magnification in the form of a colposcope or a smaller, low-powered monocular lens is another option being evaluated.

Even using traditional cytology and standard screening strategies, screening for cervical cancer is still a cost-effective intervention for public health programs. Based on World Bank

estimates of cost per Discounted Healthy Life Years (DHLY) gained, cervical cancer screening is roughly comparable in value to integrated antenatal and delivery care. If screening frequency is decreased to screen women 35 and older once in a lifetime, the cost per DHLY gained is reduced by 70%. To enhance the cost-effectiveness of cervical cancer screening, one should consider:

- Screening less frequently
- Targeting older women and high-risk populations
- Improving the accuracy of the screening test(s)
- Reducing the cost of the screening test(s)
- Using less expensive treatment strategies
- Integrating services with other health programs

As a result of PATH's review of the needs and current resources available, we propose three general strategies to suit countries at three different levels of economic and health infrastructure development. For **low-income countries** with limited urban services and scattered rural services (e.g., Ghana, Bangladesh), efforts should focus on:

- Assessing the need for screening services
- Educating policy makers about cervical cancer
- Implementing a cytology-based pilot program to demonstrate that women will accept screening, that sufficient numbers of high-grade dysplasias can be identified, and that cost-effective treatment can be provided.

For **lower-middle income** countries with adequate urban services and limited rural services (e.g., Dominican Republic, Egypt, Thailand, Zimbabwe), it is feasible to:

- Initiate a targeted screening program in a limited area that concentrates on high-risk women, screens women only once, integrates screening into existing health services, and informs targeted women of the need for and availability of services
- Establish an appropriate in-country cytology facility.

For **middle-upper income** countries with good services in urban areas and basic services in most rural areas (e.g., Brazil, Costa Rica, Malaysia, Mexico, South Korea), programs should focus on:

- Improving overall program participation
- Reevaluating the recommended screening interval and age at first screening
- Improving the efficiency and accuracy of cytology laboratory services
- Improving the availability of appropriate diagnostic and treatment services
- Increasing outreach through better IEC programs
- Refining information systems for service delivery and cervical cancer data collection.

These recommendations represent a starting point for discussions at both national and international levels. Current programs should be examined to ensure a rational use of resources. Policy makers need to be educated about the problem of cervical cancer in their countries and about how feasible, public health-oriented approaches to prevention can reduce incidence and mortality. Specific prevention approaches will vary according to the socioeconomic development of a country and the capacity of the health care system to sustain good quality care. With more attention being focused on this largely preventable cancer, we can find new hope that countries will soon be able to reduce the impact of this disease on women's lives.◆

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3. Cervical Cancer Screening: Role of Human Papillomavirus (HPV) Testing

Robert Kurman, MD

Dr. Leo Koss, a world renowned cytopathologist, refers to the Pap smear as "a triumph and a tragedy" — a triumph in that the incidence of cervical cancer has been reduced by approximately 75% from the 1940s to the 1980s, and a tragedy because this tumor, which is entirely preventable, has not yet been eradicated.

There are 17,000 new cases of cervical cancer each year in the U.S. and 7,000 deaths from this disease. Recent studies from Great Britain, New Zealand, Australia, and Canada have shown a slight increase in the incidence of cervical cancer. On a global scale, it is the leading cause of death in many countries in Latin America, Asia, and Third World nations. To try to put this into perspective, cervical cancer and its preinvasive lesions will be considered from a number of standpoints:

- Terminology and classification
- Natural history
- Screening, diagnosis and treatment

Finally, the role of the detection of the human papillomavirus in management of low-grade lesions will be discussed.

The first attempt to develop a uniform nomenclature for preinvasive lesions was made at the First International Congress on Exfoliative Cytology, held in Vienna in 1961. In the terminology that was proposed at that time, lesions were divided into two categories: CIS and dysplasia. CIS was defined as "only those cases which in the absence of invasion show a surface lining and epithelium which throughout its whole thickness, no differentiation takes place." Dysplasia was defined as "all other disturbances of differentiation of the squamous epithelial lining of surface or glands." Cytopathologists and pathologists utilize this concept of differentiation in the diagnosis of preinvasive lesions. This led to the two-disease paradigm — lesions classified as dysplasia were thought to have the potential to regress, persist or progress; whereas CIS, for the most part, progressed to invasive carcinoma. This was based on a number of studies that demonstrated that 54.6% of mild dysplasia regressed, 26.6% persisted as mild dysplasia, 18.8% advanced to moderate dysplasia, 10.4% advanced to CIS and 1.3% to invasive cancer (Christopherson, 1977).

Based on a study by Richart and Barron (1969) in which patients with Pap smears of all grades of dysplasia, from very mild through severe, were followed without biopsy, it was found

that all of these lesions progressed to CIS. Accordingly, the terminology of cervical intraepithelial neoplasia (CIN) was introduced which proposed that dysplasia was a spectrum of disease, and that all lesions, from mild dysplasia (CIN I) to CIS (CIN III), progressed.

Not all researchers agreed, however. In the early 1980s, Nasiell et al. (1983) attempted to replicate the Richart and Barron study (**Table 3.1**). In a subset of 519 patients with moderate dysplasia, they compared patients who had been biopsied to those patients in whom no biopsy was performed. Even in those who had no biopsy, a significant number of lesions regressed or persisted, not all progressed. In another study from the same group, it was found that in women with mild dysplasia, 60% of lesions regressed, about 24% persisted, and 16% progressed to CIS (Roger, Nasiell, 1986). Accordingly, most investigators feel that the behavior of dysplasia, particularly mild dysplasia, is unpredictable.

Table 3.1

FOLLOW-UP OF PATIENTS WITH MODERATE DYSPLASIA AFTER THREE ABNORMAL SMEARS (N = 519)

	Biopsy	No Biopsy
Regression	168 (50%)	53 (28%)
Persistence	66 (19%)	42 (22%)
Progression	104 (31%)	94 (50%)
Total	338	189

Nasiell et al. *Obstet Gynecol* 61:609, 1983

In 1988, a National Cancer Institute-sponsored workshop proposed a new classification system, the Bethesda System for Reporting Cervical and Vaginal Cytology ("The Bethesda System"), in which the terminology has been altered again (**Figure 3.1**) (JAMA, 1989, 1992). Now there are only two categories: (1) Low-grade squamous intraepithelial lesions (SIL) which subsumes mild dysplasia (CIN I) and lesions which show evidence of human papillomavirus change only; and (2) high-grade SIL, which subsumes moderate dysplasia/ CIN II, severe dysplasia/CIN III, and CIS/CIN III. The changing terminologies reflect in part the problem that pathologists and cytopathologists have in grading these lesions. A significant degree of irreproducibility has an important impact not only in scientific studies, but also on patient management. The management of a patient with an abnormal Pap smear is summarized as follows:

Figure 3.1

THE 1988 SYSTEM FOR REPORTING CYTOLOGICAL DIAGNOSES OF SQUAMOUS CELL ABNORMALITIES

- Atypical squamous cells of undetermined significance
- Squamous intraepithelial lesion (SIL)
  - Low-grade SIL, encompassing:
    - Cellular changes associated with HPV
    - Mild dysplasia/CIN I
  - High-grade SIL, encompassing:
    - Moderate dysplasia/CIN II
    - Severe dysplasia/CIN III
    - CIS/CIN III
- Squamous cell carcinoma

- Based on colposcopic evaluation, the gynecologist determines whether there is a normal transformation zone; an abnormal transformation zone; or the colposcopic examination is unsatisfactory, in which case a cone biopsy will be performed.

- If the colposcopic examination is satisfactory but abnormal, a directed biopsy is performed to rule out invasive cervical cancer and to distinguish benign lesions that may mimic preinvasive lesions.

- Treatment is then based primarily on the location and extent of the intraepithelial lesion. High-grade CIS lesions are ablated by cryosurgery, laser surgery, or excised by LEEP (Loop Electrosurgical Excision Procedure) or cone biopsy. Low-grade lesions reflecting the mild dysplasia (CIN I) lesions are somewhat controversial in terms of their management. Some gynecologists follow these patients, whereas other gynecologists ablate the lesions.

A number of important questions now face us about the management of the abnormal Pap smear. Are we reducing the incidence and mortality of cervical cancer at some cost? The basic plan that has been put into effect, and has been effective in reducing the incidence of cervical cancer, has been aimed at essentially eradicating intraepithelial lesions. Many of these intraepithelial lesions, if followed without intervention, would regress spontaneously. We are, in essence, using a cannon to kill a fly. We are over-treating a large number of patients in an effort to reduce the risk of cervical cancer. This strategy has been only partially effective.

Most methods of treatment are relatively innocuous. However, there are problems with cone biopsies and cryosurgery — cervical stenosis, infertility, increased frequency of miscarriages in patients in whom much of the cervix has been distorted as a result of these forms of treatment — and of course, there is the cost to the whole health care system.

Focusing now on other techniques that can be used to screen patients with cervical cancer, specifically the detection of papillomavirus, let us first consider a very important issue, again getting to the root of the triumph and tragedy of cervical cytology screening. On the one hand, we have made an enormous impact on reducing cervical cancer by cytology screening and intervention. On the other hand, as attested to by articles in the *Wall Street Journal* and *Washington Post*, patients now feel that they have been sold a false bill of goods; they had been led to believe that if they had an annual Pap smear, they would not have to worry about developing cervical cancer and that is not true. To a very large extent, unfortunately, that was the problem of physicians. Although we were aware of it, we were not communicating to our patients that there was a significant risk of a false-negative smear. The false-negative rate ranges from 5% to 50%, but the general figure that is quoted is 20%.

Finally, studies have shown that with the technique of Southern blot hybridization, papillomavirus DNA can be found in 90% of all SIL (both low- and high-grade) and 90% of invasive squamous carcinomas. But, the picture is becoming quite complex. Over 60 HPV types have been identified. They can be grouped into three categories of oncogenic potential:

- Low-risk papillomavirus which generally are limited to low-grade intraepithelial lesions and rarely, if ever, in invasive carcinomas.

- Intermediate risk viruses which tend to be found in low-grade and high-grade SIL but in a small percentage of carcinomas.

- High-risk viruses, specifically HPV-16 and 18 which make up about 70% of the isolates in cervical cancer but are also detected in low- and high-grade SIL.

Preliminary studies have now shown that in patients who are referred for an abnormal Pap smear, the presence of a high-risk HPV correlates very closely with the presence of SIL, and in fact, the presence of a high-risk HPV is more likely to indicate the presence of SIL than a repeat

Pap smear. More importantly, a repeat Pap smear and an HPV test appear to be able to identify all cases of SIL. Prospective clinical trials will be necessary to confirm whether the presence of high-risk HPV can be used in the management of an abnormal Pap smear.◆

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4. Treatment of Preinvasive Cervical Lesions
Janet S. Rader, MD

In the United States and most developed countries, the standard screening test for cervical lesions is the Pap smear. After this initial level of screening, patients with abnormal Pap smears undergo colposcopic examination of the cervix. In such examinations, the cervix is magnified 4 - 16 X times which allows for an accurate biopsy of abnormal areas to be performed. When a lesion has been identified on the exocervix and invasive disease has been ruled out, local therapy is then appropriate. Localized forms of treatment include cryotherapy, carbon dioxide laser ablation, electrocautery ablation, and LEEP.

Cryotherapy

Cryotherapy involves freezing the cervix, using either carbon dioxide or nitrous oxide as the refrigerant (**Figure 4.1**). The gas is delivered to the lesion through a gun-type unit equipped with a selection of interchangeable probes. Each probe is shaped to conform to a differently shaped cervix or lesion. When performing cryotherapy, high pressure compressed gas travels from the gas cylinder into the expansion/freezing chamber of the gun. The gases become cooled to cryogenic temperatures of between -20°C and

Figure 4.1

CRYOTHERAPY

- ◆ **Technique**
  - **Thomson Principle - temperature drop caused by sudden expansion of compressed gas through a small aperature**
  - **Carbon Dioxide or Nitrous Oxide**
  - **Probe temperature -83°C (min. -70°C)**
  - **Ice ball 3 - 5 mm beyond margin of lesion**
  - **Soluble gel lubricant - provides cold conduction**
  - **3 min. freeze - thaw - 3 min. freeze**
  - **5 min. freeze cycle**
  - **≥ 3 min. freeze until at least 4 mm thick iceball**
- ◆ **Benefits**
  - **Inexpensive**
  - **No additional equipment necessary to remove plume**
  - **Can be performed safely during pregnancy**
- ◆ **Disadvantages**
  - **10 - 14 day watery vaginal discharge**
  - **Lack of precision and difficulty in determining the exact amount of tissue that will ultimately be destroyed**

Table 4.

CRYOTHERAPY

Study	No. CIN I/II Patients	No. CIN III Patients	Median Follow-Up	Response Rate (CIN III) %
Townsend, 1983	47	53	1 year	89 (87)
Jordon, 1985	295	416	20 mths.	95
Frenczy, 1985	116	31	4 years	96 (93)
Gunasekera, 1990	61	40	6 mths.	92 (93)
Higgins, 1990	152	101	18 mths.	89 (86)
Paraskevaidis, 1991	538	1592	4 years	94 (94)
Benedet, 1992	896	915	1 year	93 (91)

-89°C at the probe tip, which causes necrosis of tissue, in this case, cervical lesions. Carbon dioxide is a common, inexpensive and safe gas costing about 50% less than nitrous oxide and should be used "bone dry" or "medical grade" since contaminants affect the freezability of the cryosurgical equipment. Nitrous oxide is more expensive but has a superior freezability (-89°C versus -68°C for carbon dioxide). In terms of treatment technique, the refrigerant is applied continuously for a 3-minute freeze, followed by a 5-minute thaw and then another 3-minute freeze. Called the "double freeze" technique, this procedure is easily performed without anesthesia. An improvement of 10% in cure rates has been shown for double versus single freeze techniques (Bryson, 1985; Schantz, 1984). In practice, a water-based surgical lubricant is placed on the tip of the probe to make even contact with the cervix. In addition, the ice ball forming on the cervix must be at least 4 mm thick and extend outside the lesion by 3 - 5 mm. When performed in this fashion for lesions as advanced as CIN III, a cure rate of over 90% has been noted in the literature. **Table 4.1** lists a number of studies which have investigated the effectiveness of cryotherapy. The main disadvantage of cryotherapy is a profuse, watery discharge that begins post-procedure and lasts about two weeks. Of note, this procedure has been performed safely in pregancy and does not appear to affect subsequent fertility or labor.

CO_2 Laser

The carbon dioxide laser requires the use of very expensive equipment to amplify and direct light waves to the cervix. The laser causes a rapid increase in tissue temperature to 100°C causing vaporization of intra- and extracellular water. The laser allows precise destruction of the cervical lesions under local anesthesia and has no associated vaginal discharge. However, not only is the initial equipment outlay expensive, but the smoke plume resulting from the use of CO_2 is a health risk to those working in the room and a smoke evacuating system is necessary. The main complication of this procedure is a 4.8% rate of cervical bleeding. **Table 4.2** lists studies which have compared the effectiveness of the CO_2 laser procedure to cryotherapy and, in one study, electrocautery. Although used extensively in the industrialized countries over the last decade, laser treatment of cervical lesions has become markedly less common as electrocautery techniques have become more widely available.

Table 4.2

TREATMENT FOR CIN: Randomized Trials

Study	No. CIN I/II Patients	No. CIN III Patients	Median Follow-Up	Response Rate (CIN III) %
Townsend, 1983				
laser	47	53	1 year	89 (87)
cryo*	47	53		93 (90)
Kwikkel, 1985				
laser	35	16	18 months	71 (81)
cryo	38	12		86 (92)
Berget, 1987				
laser	78	25	9 months	90 (96)
cryo	79	22		91 (86)
Gunasekera, 1990				
laser	61	40	6 months	92 (93)
LEEP	60	38		95 (95)

*18-mm flat tipped probe, single long freeze, thaw cycle

Electrocautery

Electrocautery of the cervix is performed by providing for the passive transfer of heat from a hot object to the tissue. Older, less commonly used electrocautery units use a "spark-gap" type electrode to fulgurate and destroy cervical tissue. This causes both uterine contractions and intense heat transfer to the vagina which is extremely painful and requires anesthesia. In a recent innovation, the Semm cold coagulator, which employs a different means of heat transfer, has been used by some institutions in Europe with minimal pain and complications. The overall success rate with this technique is over 90% (Gordon, 1991; Loobuyck, 1993).

Excision of cervical lesions by LEEP is accomplished by applying a very high frequency alternating current and thin wire loop electrode to the cervix. This technique has a unique advantage over most laser and other destructive techniques in that a specimen for pathologic review can be provided. Since this is a relatively new technique there are few large studies describing long-term success rates or any effects on subsequent fertility (**Table 4.3**).

Like cryotherapy, it can be performed under local anesthesia with minimal discomfort. Unfortunately, the required equipment is relatively expensive

Table 4.3

LOOP ELECTROSURGICAL EXCISION PROCEDURE (LEEP)

Study	No. CIN I/II Patients	No. CIN III Patients	Median Follow-Up	Response Rate (CIN III) %
Prendiville, 1989	37	64	18 mths.	95 (98)
Whiteley, 1990	33	40	3 mths.	95
Gunasekera, 1990	60	38	6 mths.	95 (94.7)
Bigrigg, 1990	659	272	4 mths.	96
Luesley, 1991	175	228	6 mths.	96 (96)
Wright, 1992	96	35	9 mths.	94 (94)
Keijser, 1992	78	32	4.8 years	82 (31)

and consists of an electro-surgical generator, a smoke evacuating system, and disposable wire loops (or reusable but with minimal reuses). The main complication is a 4% perioperative bleeding rate.

Summary

In summary, a variety of techniques are available for outpatient, localized treatment of the pre-cancerous cervix. Success rates are comparable, but capital expenses, maintenance costs, need for anesthesia, and complication rates vary considerably. Although cryotherapy has become less commonly performed in the United States in recent years, this has more to do with the attraction of physicians to "high-tech" equipment than with failure of this lower tech, but much less expensive, technique. LEEP procedures have the single advantage of being able to provide a pathology specimen but if treatment is being performed, cryotherapy offers satisfactory cure rates with a good cost-benefit ratio for lesions which have a low likelihood of being cancerous.◆

5. Cervical Cancer Screening in Thailand

Kobichitt Limpaphayom, MD

Since World War II, advancements in medical and public health services in Thailand have led to a decrease in the incidence of infectious diseases and of some diseases that can be prevented by vaccination. Female life expectancy has increased while the mortality rate has markedly decreased. There has also been a change in the cause of death among the Thai female population. Between 1983 and 1987, carcinoma was the third leading cause of death with a mortality rate of 17.8 per 100,000 women. And, statistics show that death from carcinoma of all types in women doubled from 10.5 to 24 per 100,000 between 1970 and 1980.

The most common carcinomatous lesion in women in Thailand is carcinoma of the cervix. Between 1971 and 1980, carcinoma of the cervix consitituted 31% of all carcinomas in females. According to the National Cancer Institute, the number of cases has continued to increase (**Table 5.1**).

The increasing number of cases of carcinoma of the cervix led the Ministry of Public Health (MOPH) to agree upon a strategy for early detection. This should lead to a decreasing number of advanced cases.

Table 5.1

CASES OF CERVICAL CANCER IN THAILAND 1981-1983

Year	Number of Cases
1981	2317
1982	2390
1983	2815

Policy and National Strategy

Pap smears have existed in Thailand for more than 30 years, but unfortunately, they are performed only in tertiary or secondary health centers (such as the University Hospital or large provincial hospitals). Thus, Pap smears are not available to the majority of the population living in district or remote areas. Importantly, these areas consitute two-thirds of the country's population.

The Thailand MOPH established a policy of early cancer detection in 1989 by setting up Pap smear centers in various parts of Thailand. This screening is integrated into family planning services so that most nurses are trained to perform Pap smears, especially those who have received IUD training (which has existed in Thailand since 1975).

A pilot project of early cervical cancer detection was started in 1989 with the goal of reaching at least 20% of women aged 30-60. In 1991, the service was expanded throughout the country to 61 out of 75 provinces and, at present, it covers 20%-30% of the female population between the ages of 30 and 60. Quality control is done periodically by trained medical cytopathologists.

A current problem, however, is that various institutions lack well-trained cytologists due to a "brain-drain" to the private sector and promotions within the MOPH. To alleviate this, from 1989-1993 the MOPH conducted training courses in 61 provincial hospitals (**Table 5.2**).

Table 5.2

TRAINING COURSES	
Training for Trainers	**906 persons**
District Hospital	**7,006 hospitals**
Trained Paramedical Health Personnel	**7,387 persons**
Refreshing Course for Trained Cytologists	**162 persons**

A total of 766,659 Pap smears were taken during this period, 3,731 (.5%) of which were Class III and 2,197 (.3%) of which were Class IV and V.

Chulalongkorn Hospital

In Chulalongkorn Hospital, a tertiary health center, Pap smears have been done for more than 30 years. **Table 5.3** summarizes the pap smear statistics for a five year period. As noted, smears taken at the out-patient clinic yielded proportionately more suspicious and positive cases than did the FP clinics.

In 1992, an analysis was done of false-negative smears from women with cancerous lesions of the cervix. In an examination of 330 cases proven to have cervical malignancy, only 194 were positively detected by Pap smears. Of those 194 cases, 142 cases (73.19%) were abnormal according to the cytological exam and the remaining 52 cases (26.81%) were

Table 5.3

1987-1991 PAP SMEARS

OUT-PATIENT

Year	Total	Neg-Atyp	Suspicious	Positive
1987	25855	25448	344 (1.33%)	63 (0.24%)
1988	25971	(98.43%)	427 (0.95%)	56 (0.22%)
1989	24188	25488	406 (4.68%)	69 (0.29%)
1990	25542	(94.14%)	506 (1.98%)	68 (0.27%)
1991	22482	23713	456 (2.03%)	42 (0.19%)
		(98.04%)		
		24968		
		(97.75%)		
		21984		
		(97.78%)		

FAMILY PLANNING CLINICS

Year	Total	Neg-Atyp	Suspicious	Positive
1987	9475	9424 (99.46%)	45 (0.47%)	6 (0.66%)
1988	10006	9947 (99.41%)	56 (0.56%)	3 (0.03%)
1989	10306	10228	77 (0.75%)	1 (0.01%)
1990	10910	(99.24%)	90 (0.82%)	3 (0.03%)
1991	10190	10817(99.15%)	119 (1.17%)	3 (0.03%)
		10068		
		(98.80%)		

PRIVATE OUT-PATIENT

Year	Total	Neg-Atyp	Suspicious	Positive
1987	14415	14241	166 (0.01%)	8 (0.06%)
1988	15452	(98.79%)	173 (1.12%)	8 (0.05%)
1989	16157	15271	197 (1.22%)	12 (0.07%)
1990	12447	(98.93%)	254 (2.04%)	15 (0.12%)
1991	10957	15948	77 (0.70%)	6 (0.05%)
		(98.71%)		
		12178		
		(98.84%)		
		10874		
		(99.24%)		

false-negatives. The majority of the false negatives (43 cases or 82.69%) resulted from errors in taking the smear and the rest (9 cases or 17.31%) were due to interpretation error. The results of this study led to strict quality control both in terms of how to obtain as well as interpret a Pap smear.◆

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6. Cervical Cancer Screening in Kenya

H. C. Sanghvi, MD

Although no national statistics are available to document the magnitude of the cervical cancer problem in Kenya, some data have been collected as part of hospital-based observations and research projects. Among patients presenting themselves to hospitals with the diagnosis of cervical cancer, the average age has been decreasing. In 1960, the average observed age was 46 years and by 1990 this had dropped to 40 years. Unfortunately, however, these data are not adjusted for stage of disease. A possible explanation for this change is that in 1960, with a much less urbanized population and less access to health care than is available today, the stage of disease with which patients presented was higher than today. On the other hand, it is also possible that in a society with high parity and earlier age at first intercourse, the age at which cervical cancer could first be detected has truly decreased. Highly parous patients comprise a disproportionately high percentage of patients with cervical cancer in Kenya. National statistics indicate that only 32% of women are greater than para 5 while 70% of cancer patients are of this or greater parity.

Consistent with the statistics given above, there has been some downstaging in the severity of the disease over the last few years. In 1980, almost 62% of patients were Stage 3 or greater while in 1990 this number was only 53%. In 1980, 28% were at Stage 2 compared to 35% in 1990. Unfortunately, however, less than 12% of patients presented with Stage 1, the stage at which higher rates of cure are possible and effective surgery can be performed (**Table 6.1**).

According to these data, then, only 15% of all patients presenting with cervical cancer in Kenya were considered operable and the rest required radiotherapy. There is only one radiotherapy unit available in Kenya with the result that many late stage patients do not receive treatment.

Table 6.1

STAGE OF DISEASE AT PRESENTATION		
	1980	**1990**
Stage 1	10.2	11.8
Stage 2	28.1	35.3
Stage 3	56.0	45.1
Stage 4	5.7	7.8

Although in the developed world cervical cancer is not even among the top five cancers among women, in Kenya it is the most common genital tract cancer with which women present. It represents 59% of all documented genital tract cancers nationwide. Breast cancer is a remote second (considered a genital tract cancer by some) occuring in 25% of patients (**Figure 6.1**). In terms of the age distribution, 64% of patients were between 30 and 50 years of age, and 32% of women were between ages 30 and 40 (**Figure 6.2**).

While it is generally agreed that Pap smear screening can play a role in detecting pre-cancerous lesions, it is also important to maximize the impact of initiating screening by identifying a high risk population among which the positives might be concentrated. In an effort to identify if such a population exists, screening was performed in a number of clinics in Nairobi and rural locations (**Table 6.2**).

Figure 6.1

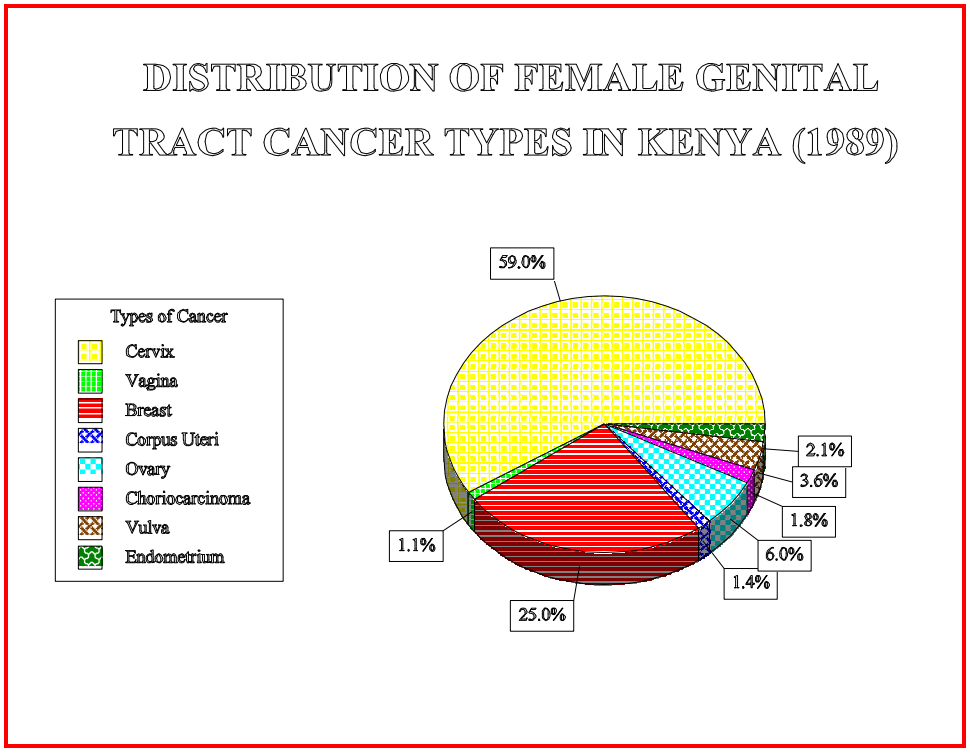

Figure 6.2

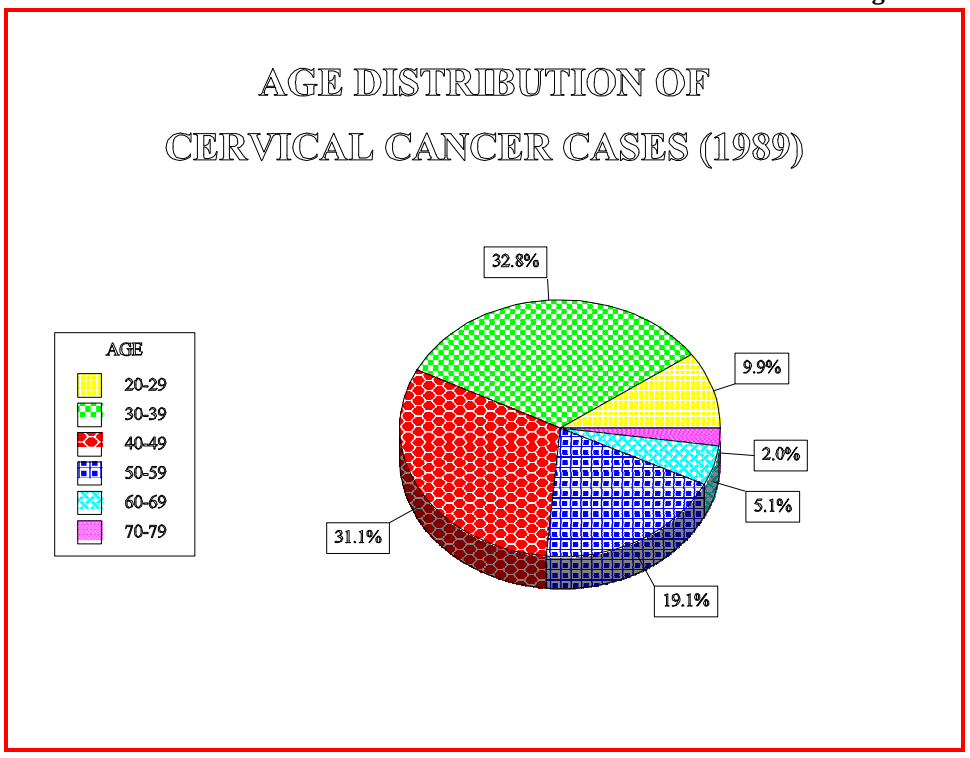

Table 6.2

PREVALENCE OF CIN BY CLINIC TYPE

NAME	SAMPLE SIZE	CIN PREVALENCE PER 1000
KNH Gynaecology Clinic	4909	20.4
KNH Antenatal Clinic	1000	10.0
KNH FP Clinic	1240	29.0
Nairobi STD Clinic	1320	14.0
Rural Community Clinics	1755	25.6
Rural FP Clinic	400	34.8
Rural Random Sample	835	26.3

According to the results of this exercise, the prevalence of CIN (of any grade) ranged from 3.5% in a rural location to 1.0% at an urban pre-natal clinic. The prevalence of CIN III was less than 5/1000.

Importantly, these data showed that parity was highly correlated with abnormal Pap smears. Abnormal smears were discovered in only 12.8% of para 0 women compared to 35.1% of women greater that para 5 (**Table 6.3**).

Table 6.3

DISTRIBUTION OF ABNORMAL PAP SMEARS BY PARITY

0	12.8%
1-2	17.9%
3-4	27.3%
5 +	35.1%

Table 6.4

DISTRIBUTION OF PAP SMEAR CLASS IN A FP CLINIC

	Prevalence per 1000
Pap Class 1	301.0
Pap Class 2	672.0
Pap Class 3	24.4
Pap Class 4	2.0

PREVALENCE OF ABNORMAL PAP SMEAR BY AGE

Age	Prevalence per 1000
15-19	4.7
20-24	26.7
25-29	34.8
30-34	24.5
35-39	29.2
40 +	28.0

The prevalence of abnormal Pap smears at FP clinics was slightly higher than in the general population. Among women between the ages of 25-29 presenting to an urban FP clinic, 3.5% of smears were abnormal (**Table 6.4**). Interestingly, in these clinics, when clients were confronted with the presence of an abnormal smear, the belief was engendered that the FP method was responsible for this change.

It has long been postulated that infection with the human papillomavirus (HPV) is what ultimately produces the cervical changes which can lead to cancer. In this investigation, the prevalence of Pap smear changes consistent with HPV infection was compared with those Pap smears with evidence of CIN. Not surprisingly, it was found that cytological evidence of HPV infection was highly correlated with Pap smears positive for CIN. The odds ratio of having CIN if HPV was present was 29.6 (95% CIN = 12.9-67.6) (**Table 6.5**).

To further elucidate this association, a series (22,648) of Pap smears taken between 1983 and 1987 were reassessed for the presence or absence of HPV infection, specifically kilocytosis. Twenty percent of these smears showed such changes, with a mean age of 35 for koilcytosis-postive women. The mean age for the koilcytosis-negative group was 46, suggesting that the cervical changes associated with HPV infection begin at a relatively early age. There was no correlation, however, with the presence or absence of HIV infection.

Table 6.5

RELATIONSHIP BETWEEN CIN GRADE AND PRESENCE OF HPV*

	NO. +HPV	NO. -HPV
CIN 0	37	1767
CIN I, II, III	13	21

*HPV found in 2.7% of Pap smears
OR = 29.6 (12.9-67.6)

With respect to cervical cancer screening, a pilot study was recently conducted for one month in Nairobi (using two FP, one STD and one gynaecology clinic) where 692 smears were obtained. Of these, 78% were considered "good quality" (20% had no endocervical cells in the smear), 6.4% were determined to be Class III (evidence of dysplasia), and 0.1% were found to have changes consistent with CIN III. Fifty-two percent of smears showed evidence of infection, the majority of which were found to be bacterial (**Table 6.6**).

Table 6.6

DISTRIBUTION OF PAP CLASS, INFECTIONS AND HPV

Pap Class	
Class III	
CIN I	5.1%
CIN II	1.2%
CIN III	0.1%
Class II	52.0%
Associated Infections Diagnosed on Smear	
Bacterial	38.2%
Trichomonas	10.8%
Candida	2.7%
Acinomycosis	1.6%
Non-specific Infection	19.9%
Specific Tests for HPV	
HPV 6, 11	0.9%
HPV 16, 18, 31, 33	9.0%

In an effort to increase the capacity to provide cervical cancer screening nationwide, 30 cytotechnicians have been trained at the University of Nairobi (using a three month competency-based curriculum) over the last several years. One year after training, their output (in terms of the number of smears read) was assessed. Ten of the trainees reported not having read any slides and 15 had read less than 500 in the year since finishing training. Only one trainee had read more than a thousand slides. Two important reasons postulated for this lack of output include:

- Materials such as reagents, slides, and reliable microscopes are difficult to obtain in areas outside the major urban areas

- Technicians are required to perform many other duties and may not have the time to devote to cyology.

As part of this follow-up assessment, the trainees were asked to submit slides (which they had read) to the reference lab at the University where they were read by a cytologist. Among the slides submitted for review, there was a high correlation with the reading of the cytologist. Sensitivity and specificity (assuming the cytologist was "truth") was 91.7 and 99.7%, respectively. The predictive value positive was also very good. This was based on a total of 800 smears among which 4.7% were Class III or higher (**Table 6.7**).

Table 6.7

TRAINING OF CYTOTECHNICIANS: QUALITY CONTROL

		Reference Lab I	II	III	IV	
Trainee	I	419	20	2	0	736
	II	31	263	1	0	
	III	0	2	30	1	35
	IV	0	0	0	2	

Sensitivity	91.7%
Specificity	99.7%
Positive Predictive Value	94.3%
Note: Prevalence	4.7%
Negative Predictive Value	99.6%

Currently, the role of the reference (Central) lab is to review all smears of the trainee technicians for one year post-training and to return all smears with instructions on how to re-read the slide (if there is a discrepancy in their findings). On-site remedial training is provided if disrepancies persist in the reading of the slides. After the first year post-training, the Central Lab will review 10% of smears read as Class I or II and all smears read as Class III or IV.

One conclusion is that although quality technicians can be trained, a variety of problems beyond their control may keep their training from being effective. Some of the rate-limiting steps included a lack of supplies and equipment. Thus, obligating a great deal of funding to the training of such personnel may not be cost-effective if they are not able to reliably put their skills to consistent use.

In a study of client perceptions in Kenya, it was found that among women who had never had a Pap smear, the vast majority stated that they would like to have a regular gynecological exam and a Pap smear. Only 61%, however, knew where a Pap could be obtained. And interestingly, the number of clients knowledgeable about cervical cancer symptoms and the relationship between cancer and screening was only in the range of 21-35%. This indicates that the public could benefit from increased information about the value of cervical cancer screening (**Table 6.8**).

Table 6.8

CLIENT PERCEPTIONS

	Had a Pap N = 135	Never had a Pap N = 106
Knows a Pap smear screens for cancer of cervix	35%	21%
Knows the symptoms of cancer of cervix	35%	34%
Believes cancer of cervix is preventable	29%	46%
Knows where a Pap smear can be obtained	82%	61%
Would like to have a regular Gyn exam	97%	93%
Would like to have a Pap smear		87%

*Nyamu, 1989

A number of strategies are envisioned in the future for improving cervical cancer screening in Kenya:

- **Downstaging—**It will be important to teach all health personnel to visualize the cervix at every opportunity. In this way, lesions which could become cancerous can be discovered and, if possible, treated.

- **Opportunistic Screening**—It is apparent that a national mass screening program based on Pap smears is not feasible. However, screening should be undertaken whenever the opportunity presents itself. Such opportunities include FP clinics, gynaecology clinics, antenatal clinics and STD clinics.

- **Training**—Schemes ranging from tertiary care (e.g., Wertheim Hysterectomy) to primary level endeavors (e.g., training nurses to *look* at the cervix as well as take a Pap smear) will need to be developed.◆

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7. Cervical Cancer Screening in Haiti

Jean-Robert Brutus, MD, MPH

Cervical cancer is a considerable public health problem in Haiti although, unfortunately, little is being done about it by health officials. As early as ten years ago, in 1984, Dr. Lionel Negrette, a Haitian obstetrician-gynecologist, observed that there was no center specializing in cancer in Haiti, not even the Haitian State University Hospital (Hôpital Universitaire d'Etat d'Haïti - HUEH) or the Maternité Isaïe Jeanty, the two main public hospitals in the capital. He theorized that the absence of statistical data on cervical cancer in Haiti reflected a lack of interest in the problem rather than the magnitude of the problem itself. The following is a summary of data that was available for presentation at this workshop.

In 1986, Mitacek, St. Vallières and Poledneck presented the results on a study cancer cases in Haiti for the years 1979-1984. The majority of these cases were:

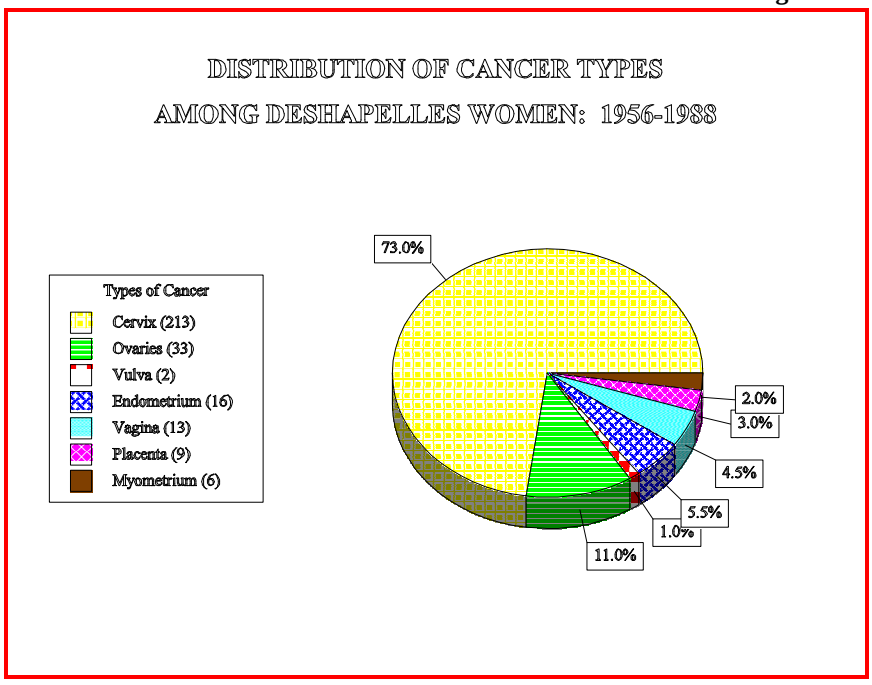
- Stomach and intestinal cancers
- Primary cancer of the liver (chiefly among the male cases)
- Cancer of the cervix
- Cancer of the penis
- Karposi's sarcoma

Also in 1986, Rachel Fruchter, Jean Claude Rémy, William Burnett and John Boice published an article in the *American Journal of Public Health* (*AJPH)*. They observed, even at that time, that Haitian women living in the U.S. presented with more advanced cases of invasive cancer of the cervix than did Hispanic American women. They noted that "invasive cancers of the cervix (ICC) among Haitian immigrants are usually diagnosed in more advanced stages than are similar cancers among women born in the United States." This, they speculated, was because asymptomatic Haitian women were not in the habit of seeking routine testing (Pap smears) and delayed seeking care even after the appearance of certain initial symptoms. Some data are

available from a cervical cancer screening study carried out in 1987 by Doctors Mondestin, Jean Boisrond, Jean-Ronald Cornely and Jean Joseph at the HUEH. They showed that of the 474 Pap smears from patients between the ages of 15 and 44 (who came for a consult because of vaginal bleeding, hypogastric pain or abdominal masses), 20.7% had suspect Class III malignancy cells.

The most exhaustive study published to date was by Dr. Vergnaud Péan, pathologist, and Dr. Jean Baptiste Michel of the Albert Schwitzer Hospital in Deshapelles. Deshappelles is a small rural community about 90 miles north of Port-au-Prince and the hospital serves a catchment area of about 180,000 inhabitants (more than 50,000 patients were seen at this center in 1988). This study covers 32 years, from 1956 to 1988. About 20,000 specimens were examined and, of these, more than 4,000 were found with tumoral pathology (4,132 cases out of 19,874 or 29.79%). Two hundred and ninety-two of the 4,132 cases (7%) were cancers of the female genital system. This study revealed that all the organs of the female genital system are subject to cancer in the population of Deshapelles with the exception of cancers of the Fallopian tubes. Cervical cancers clearly pre-dominated, constituting 70% of the cases (**Figure 7.1**).

Figure 7.1



According to the findings, exocervical malignancy exceeded endocervical tumors by 88% and endometrial cancer was rare (accounting for only 5% of all female genital cancers). Carcinoma in situ represented only 6% of all exocervical squamous carcinomas. Among this population, cervical cancers appeared in women in their early twenties with a rise in the rate for women in their forties and sixties (**Figure 7.2**). Endocervical cancer (70% of all cervical cancers) also occurred very early in women in their twenties and **Figure 7.3** shows a peak incidence among women in their forties in this population.

Dr. Péan's study showed that patients with cancer usually present too late, when the neoplastic process has already progressed outside the organ into neighboring tissues and ganglia. By this time, the cancer is inoperable. This reality was previously identified by Fruchter and

Rémy in their article published in the *AJPH* in 1986. In Péan's study, however, in situ cancers were only 6% of all exocervical squamous carcinomas.

These findings all point to the fact that cervical cancer among Haitian women is clearly a public health problem. The probable reasons for this were enumerated in an article by Sherris, et al, 1993. (See page 3 of these proceedings for reasons).

Figure 7.2

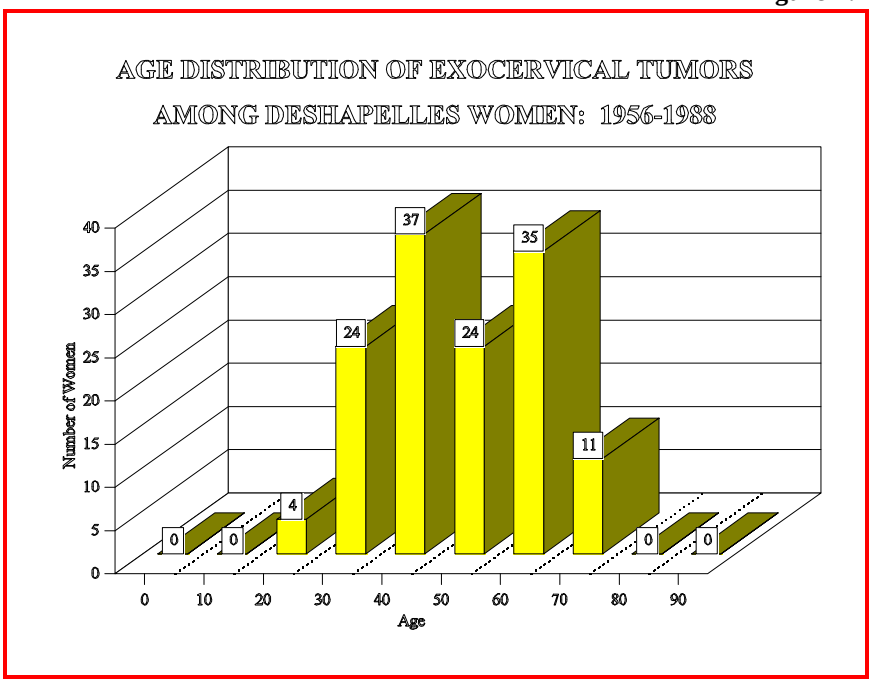
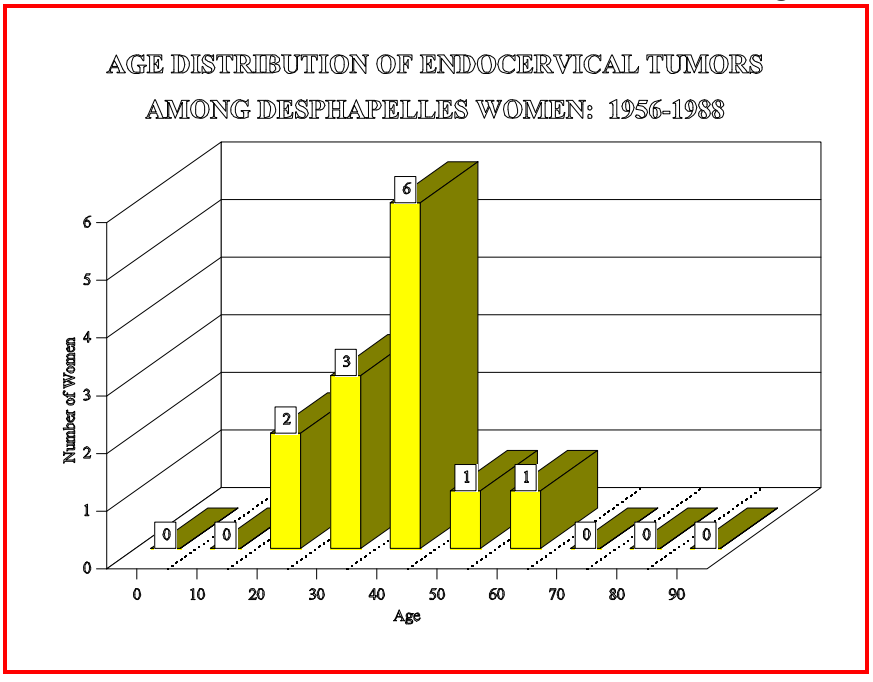


Figure 7.3



As of 1994, the infrastructure for systematic cervical cancer screening in Haiti is inadequate. There are only five laboratories specializing in Pap smear analysis and these are all in Port-au-Prince. The cost of an examination ranges from US$10 to $20. The cost of a laparoscopic (colposcopic) examination is between US$50 and $100. The only available (public) colposcope at the University hospital is currently out of order and only four other physicians in Haiti have a colposcope in their offices.

A program of early detection combined with the establishment of facilities for care needs to be provided in Haiti with a view to limiting the disease is needed. To date, lack of financial resources has limited any action of this kind so far.◆

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8. Cervical Cancer Screening in Brazil

Sylvia Bomfim-Hyppolito, MD

The Maternidade Escola Assis Chateaubriand (MEAC), a tertiary level hospital belonging to the Ceará Federal University, offers integrated health assistance to women and newborns. Both cervical and breast cancer screening are currently offered as part of the Gynecology out-patient service and in the Obstetrics ward. The hospital family planning (FP) service also offers these cancer detection procedures to all FP users.

In the hospital, Pap smears are done under supervision by post-graduate students as part of their sixth-year course. The MEAC has a cytology lab on-site, where some 15,000 slides collected locally are read annually as well as slides sent by various Ceará State Health Department counties under special agreements. The slides are read by specially trained second year technicians who identify suspicious findings for further analysis by a biochemist and physician. Patients with a physical exam considered suspicious also are referred to a higher level for assistance where they undergo a colposcopy and a biopsy (directed by colposcopy), if necessary.

Electric or cryocauterization of the cervix is indicated in the State of Ceará for Type I and II cervical intraepithelium neoplasias (i.e., CIN I - II). For CIN III and cancer in situ, conization of the cervix or hysterectomy is indicated. Referral to the Cancer Detection Institute, a specialized cancer organization in the area, is done when there is need for radiotherapy as treatment (and exclusively for IIIrd and IVth stage cases).

Despite all these resources, the State of Ceará has several counties where no doctors are available. To deal with this problem, the MEAC developed an Extension University Program in which Traditional Birth Attendants (TBAs) are trained to give primary health assistance including: pre-natal care, delivery assistance, cancer/STD detection, FP and newborn assistance. The TBAs receive training in how to perform a simple clinical exam as part of cervical cancer screening to recognize any of the following conditions:

- Normal cervix
- Reddish spot
- Easy bleeding
- Strange mass
- Ulcer

Based on the findings of the clinical exam, anything that is not considered normal is referred to the supervisor.

Training TBAs requires appropriate technology and the MEAC has recently had positive experiences in this area with technical and financial support from JHPIEGO. The JHPIEGO-sponsored program incorporates group dynamics and training techniques that fit the TBAs learning levels (the great majority of them are illiterate). The MEAC graduate nurse also has an important role in this program. She visits the primary health unit (where the TBAs are posted) twice a week to supervise the TBAs and reviews all risk cases referred by them. The nurse reexamines the referred cases and performs the Schiller Test (using an iodine solution) to screen for abnormal cervical tissues. Acetic acid is used before the test is done to clear away the cervical mucus (not as a screening technique) in cases where the colposcope is not being used. In addition, a MEAC medical doctor visits the primary health unit once a week and reviews all of the nurse referral cases. He can biopsy anyone found to be abnormal from the Schiller Test assessment and refer to the MEAC any cases that need treatment.◆

9. Methods of Cervical Cancer Screening

Paul D. Blumenthal, MD, MPH

Although cervical cancer is almost always preventable through the introduction of practical, sustainable screening programs, at present there are few, if any, successful, self-sustaining, long-term cervical cancer screening programs in the developing world. Such a screening program could appreciably reduce and ultimately eliminate most of the morbidity and mortality from cervical cancer.

Although the Pap smear is widely accepted as the primary cervical cancer screening test, this is due more to the fact that it has been widely available in developed countries than to its efficacy in these settings (scientific merit). Although the Pap smear can be acceptably sensitive and specific as a screening technique, Pap smear **systems** are expensive, require constant fine tuning, and are difficult to maintain. This is particularly true in developing world settings where resources and trained personnel are scarce. In this regard, there are a variety of alternative screening methods available, of which some form of visual screening offers considerable promise for developing countries.

Papanicolau Smear (Pap smear)

In countries with resources and a sophisticated medical system capable of maintaining the technology, the use of cervical cytology (i.e., Pap smears) has proved successful. In most countries of the world, however, such resources are rarely available. Furthermore, the establishment of a sustainable Pap smear screening program entails considerable training of the technicians (cytologists), as well as the maintenance, capital, and logistic costs. In addition, there are a number of "steps" involved in fixing and staining a Pap smear before it can be read under the microscope. If any one of these steps fails, or is not done correctly (due to lack of supplies, equipment or trained personnel), the whole screening program is rendered ineffective. Another major problem with Pap smears is that the results cannot be made available while the client is still in the clinic. Frequently, the turn-around time is up to a week — and much longer in those developing countries where limited Pap smear services are available. As a consequence, follow-up of women with abnormal Pap smears often never happens because they can not be located or there are no funds for an outreach program.

The goal of a comprehensive screening program should be to target as many women as possible in the 35-40 age range where advanced precancerous lesions (but not invasive cancer) are most likely to occur. In some countries, such as those with a high incidence of STDs and HIV, screening from a younger age (e.g., 30-35) may be warranted. Screening can be relatively infrequent (e.g., every 10 years or once per lifetime where resources are limited) and still offer significant public health benefits. In some areas, the Pap smear will be the screening method of choice. For those selecting this method, many now recommend that endocervical brushes replace cotton-tipped swabs as a means of collecting endocervical cells for the smear. While this technology enhances the collection of cells, thereby reducing the need for repeat smears and possibly the overall cost of screening, it is significantly more expensive per individual smear. The method of air-drying smears (rather than fixing with commercial spray fixatives or

immersion in 95% ethyl alcohol) has been used successfully in one program with considerable cost savings.

Even under optimal conditions, however, Pap smears may fail to detect cervical cancer and its precursors 15 to 40 percent of the time. Although colposcopy is now considered a **diagnostic** test, when it was introduced in 1924 by Hinselmann, it was considered to have potential as a **screening** tool. Unfortunately, however, early colposcopes were awkward, very expensive and not suitable for screening. On the other hand, when used as a diagnostic test, colposcopy, in association with biopsy of abnormal area, has very good sensitivity and specificity and is considered by many to be the "gold standard" against which the Pap smear is judged.

In many settings, a less costly, simpler screening method may be necessary. Approaches that are currently being evaluated include unaided visual inspection of the untreated cervix to detect early stage cancer and aided visual inspection of acetic-acid treated cervix. Preliminary published data from India, Italy and the U.S. indicate that unaided visual inspection of the cervix may detect about two-thirds of early cancers.

Cervicography

Cervicography, first developed by Staffl, is a more recently developed visual screening tool (**Figure 9.1)**. The essence of cervicography consists of taking a photograph of the cervix and projecting it at high magnification. The photographs are processed and analyzed at a central facility. Thus, cervicography could be considered a a form of "distance colposcopy" but without the capacity for biopsy. Most commonly used in conjunction with cytology, cervicography has approximately 80% sensitivity but rather low specificity (approximately 50%). Although cervicography meets many of the basic criteria of a good screening test (e.g., it is painless, easy to use, provides documentation, and has good sensitivity), it has a number of disadvantages, particularly where developing countries are concerned. Most important of these is the need for special equipment (e.g., a camera) which can easily break and which is difficult to replace.

Figure 9.1

CERVICOGRAPHY

- **Advantages**
  - Painless
  - Easy to use
  - Provides documentation
  - Highly accurate results
- **Disadvantages**
  - Special equipment needed
  - More expensive than cytology
  - Less specific
  - Laboratory far away
- **Costs**
  - Cervixscope $2,150.00
  - Transformer 350.00

In recent years there has been increasing interest in visual screening of the cervix as an adjunct to cytology. Studies exploring its usefulness have concentrated on either naked-eye visual screening or screening involving a low power magnifying device. In either instance, acetic acid is commonly used to assist the observer in revealing abnormal cervical tissue.

Low-Power Optical Cervical Screening

In a small series of 309 patients, Abrams, using a small monocular magnifying device with a power of 2.5 which he termed the "Gynoscope," showed a sensitivity and specificity comparable to the Pap smear (87% and 84%, respectively). This method of screening involves visually assessing the cervix as a means of *pre*cancer screening through the use of the relatively inexpensive ($95), hand-held, low magnification device/telescope (**Figure 9.2**). Used to view untreated and 2.5% acetic acid-treated (vinegar) cervical tissue, this type of visual screening system allows trained observers to quickly (on-the-spot) and easily identify abnormal tissue for biopsy and more importantly, treatment. If data such as Abrams' hold up as other more rigorous studies are conducted, the Gynoscope has a number of potential uses. For example, it is small, inexpensive and sturdy. Either used alone or in conjunction with cytology, it can be used to identify cervical lesions, either for purposes of biopsy or treatment. Importantly, as is true for any visual method, results can be given to the patient immediately.

Figure 9.2

GYNOSCOPY

- **Advantages**
  - Easy to use
  - Portable
  - Inexpensive
  - Permits lesion identification in conjunction with Pap smear
  - Can enhance patient cooperation
- **Disadvantages**
  - Training is necessary
  - Low magnification
  - Precision and specificity not well established
  - Does not replace colposcopy
- **Costs**
  - Gynoscope $95.00

While visual screening meets the requirements of a good screening test (e.g., is not invasive, is easy to perform, inexpensive, and has acceptable rates of false positives and negatives), compared to the Pap smear, it has several advantages which are particularly important in the developing world:

- It can be performed by almost anyone, in almost any setting. The only equipment needed is a light source, a speculum, a source of acetic acid (household vinegar) and optionally a Gynoscope.

- Results are apparent immediately. Therefore, it is possible also to provide initial treatment at the time of examination. Thus, there are no mandatory breaks in the system between diagnosis and treatment.

- With the exception of the Gynoscope (which may or may not be necessary), all of the components of this system are available locally. There are no imported reagents and no expensive electronic equipment.

Visual screening has been shown to be practical and effective in identifying the abnormal and pre-cancerous cervix in a number of studies (Sehgal et al, 1991; Ottaviano and La Torre, 1982). In a study of 2,500 women aimed at determining whether observers could detect a normal or atypical squamo-columnar junction with the naked eye, Ottaviano and LaFlore, working in Italy, had excellent results. They reported that for the purposes of identifying the transformation

zone and determining whether it was normal, visual screening (assisted by acetic acid staining) was equivalent to the colposcope. In India, visual screening with the naked eye without acetic acid detected 52% of cases of CIN III which would have gone undetected had visual screening not been available at all. Although in cytological terms a sensitivity of 52% is not acceptable, this figure represents what can be done with no instrument other than the naked eye just by taking the time to **look** at the cervix.

In an unpublished preliminary pilot project in Baltimore, Blumenthal demonstrated a specificity of 98% when visual screening with the naked eye was compared to the Pap smear (where the Pap smear was used as the "gold standard") (**Table 9.1**). Because there were few truly "positive" cases in this patient population, the sensitivity was low (28%). The positive predictive value, however (using colposcopy as the gold standard), was approximately 60%. Larger populations with more positive cases are needed to better determine the sensitivity. An ongoing study in Indonesia by PATH is attempting to answer some of these questions, and preliminary results are encouraging.

Table 9.1

FRANCIS SCOTT KEY MEDICAL CENTER
VISUAL SCREENING STUDY 1993
N = 83 (43 Routine/40 Referred)

Predictive Values		**Pap Smear**		
		Abnormal	**Normal**	**Total**
Visual	**Abnormal**	***50.00***	50.00	100.00
	Normal	5.13	***94.87***	100.00

Sensitivity/Specificity		**Pap Smear**		
		Abnormal	**Normal**	**Total**
Visual	**Abnormal**	***20.00***	1.33	2.5
	Normal	80.00	***98.67***	97.50
	Total	100.00	100.00	100.00

The question of training and who can perform this kind of screening is crucial to the ultimate acceptability of this method. Van Le et al recently demonstrated that given brief training in the essentials of recognizing cervical abnormalities, nurse practitioners could consistently and successfully screen the cervix visually. Although the false positive rate was high (40%), indicating a definition of "positive" that was perhaps too strict, the observers were able to detect 15% more cases of CIN and 26% more cases where koilocytosis was seen, than did the Pap smear.

Summary

Although it is clear that visual screening systems have potential application in many countries, it has not yet been tested in developing world settings, nor on a large scale anywhere in the world. Based on the results of the studies that have been conducted, however, visual screening combined with acetic acid preparation of cervical tissue warrants further investigation as a cost-effective way to identify women in developing countries with cervical (especially early) lesions. Furthermore, when combined with low-cost treatment regimes (e.g., cryotherapy), it also may provide the opportunity for on-the-spot treatment capability — a distinct advantage over other cervical cancer screening methods.

In summary, visual screening of the cervix using either the naked eye or assisted by low-power magnification holds considerable promise for countries which are financially resource poor. Many of the disadvantages of systems which rely either on imported technology or expensive equipment are obviated and patients who require either treatment or referral can be

given such immediately. As further studies better document the sensitivity, specificity and predictive values of these techniques, their applicability for use in national or regional level screening programs will be better understood.◆

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10. PATH Indonesia Cervical Cancer Screening Study

Vivien Davis Tsu, PhD

Visual inspection of the cervix after staining with acetic acid has been suggested as an alternative approach to cytology when used with some form of magnification. PATH has identified a small, lightweight, monocular lens called the Gynoscope, which has been developed by a U.S. gynecologist as an alternative to a colposcope for enhancing visual inspection of the cervix. As no independent international evaluation of this device had been conducted, PATH has undertaken an evaluation of Gynoscope-aided visual inspection in Indonesia, in collaboration with the Indonesian Cancer Foundation (YKI) and Yayasan Kusuma Buana (YKB), a private nonprofit health and family planning organization in Jakarta.

Study Objectives

The study was designed to assess the feasibility and acceptability of visual inspection using the Gynoscope as a cervical cancer screening tool. The objectives of the study are to:

- Assess the accuracy of visual screening using the Gynoscope as compared to Pap smears in identifying normal cases, mild dysplasia, moderate-severe dysplasia (e.g., treatable, pre-cancerous lesions), and suspected carcinoma in situ or invasive cancer (referrals)
- Assess the acceptability of the Gynoscope to clinicians
- Determine the level of prior clinical training/background necessary to use the Gynoscope successfully
- Determine the appropriate type and amount of training needed to do visual inspection successfully aided by Gynoscopy
- Determine the appropriateness of two potential settings for Gynoscopy

Methods

Preliminary Assessment and Training

In November 1992, a PATH team (including Dr. Paul Blumenthal as medical consultant) traveled to Indonesia to conduct a three-day workshop and training focusing on the feasibility of using visual inspection of the cervix enhanced by the Gynoscope. The specific objectives of the assessment were to:

- Present an overview of cancer screening techniques to a select group of Indonesian medical personnel representing a variety of health care organizations

- Train master trainers in the use of the Gynoscope and/or naked-eye visual screening techniques

- Develop a research protocol to assess the usefulness, sensitivity and specificity of visual inspection with and without the Gynoscope for cervical cancer screening in comparison to Pap smears which are currently used

Preliminary activities included a two-day physician orientation on the use of the Gynoscope at YKI's Early Detection Center and a one-day nurse-midwife orientation at a YKB clinic. While only a few physicians attended, nurse-midwives from all six YKB clinics attended the YKB orientation. The objective of the orientation was to assess the training needs of service providers in cervical cancer screening using the Gynoscope.

Training of Physicians

The physicians were comfortable using the Gynoscope as they had considerable experience with the colposcope and a good grasp of cervical examination. They could reliably identify a "negative" cervix. In terms of their preliminary acceptance of alternative cervical cancer screening methods, the physicians in attendance felt that visual screening could play an important role in the provision of health care in Indonesia. They felt that if its efficacy could be established, the approach could be particularly useful where Pap smear services are unavailable, for example, outside urban areas and in the outer islands. Strong objections were expressed, however, about the possibility that health care providers other than doctors might be able to perform the screening.

The techniques of both Gynoscopy and naked-eye screening were presented, and it was agreed that naked-eye screening should be integrated into the study (although it was not actually included in Phase I). As a consequence, a number of recommendations were made during the initial assessment visit regarding the future training of physicians in cervical cancer screening with a Gynoscope. These included:

- Determining what aspects of cervical pathophysiology need to be understood (especially by lower-level health care personnel) in order to be able to perform visual cervical cancer screening proficiently

- Developing a curriculum and use media and methods appropriate to the trainees to communicate the necessary information

- Determining how the attributes of a positive and negative screening results can be conveyed to others (i.e., what types of visual aids would be required for optimum training such as slides, transparencies, models, posters, or atlases)

- Determining the appropriate length of training time and the means to be used to evaluate the training as well as its long-term impact

Training of Nurse-Midwives

The nurse-midwives trained at YKB were very interested and enthusiastic about visual inspection techniques. The information presented was effectively communicated and absorbed, but it seemed that special approaches focusing on terminology and basic knowledge need to be included whenever training of personnel such as midwives occurs. The training session with the midwives at YKB was more extensive than the one held at YKI. While the midwives were less familiar with the principles of cervical examination than the Ob/Gyns at YKI, they already had some experience in naked-eye visual inspection of the cervix (as evidenced by YKB's patient record form which requires that the condition of the cervix be recorded based on visual inspection). As the clinical training progressed, the midwives became increasingly confident in recognizing an abnormal (or minimally diseased) cervix and an atypical one (e.g., trauma from childbirth, inflammation, ectropion). Recognizing a truly positive lesion, however, may be more difficult. Nevertheless, it seemed quite clear that, at the very least, Gynoscopy could be used to differentiate those who are clearly normal from those who might benefit from a Pap smear.

Phase I

As a result of the concerns raised during the preliminary assessment, it was decided to divide the study into two phases. The first phase would allow the gynecologists at YKI to carry out a smaller-scale assessment of the technique's sensitivity and specificity before an evaluation with nurse-midwives. This phase, for which YKI had primary responsibility, was carried out in YKI's Early Detection Center for Cancer and in YKI's main outpatient clinic in central Jakarta. This phase was to take three to six months, depending on the prevalence of "positive" cases. Ultimately, it took approximately nine months to complete.

Sample size

It was determined that at least 24 positive cases (CIN III or worse) would be needed to estimate a sensitivity of at least 90% at the 95% confidence level. At an expected prevalence of 1% disease in the population, 2400 women would need to be screened to yield the desired number of positive cases. When enrollment went more slowly than planned, it was agreed that Phase I would be complete as soon as 24 positives had been identified.

Participant eligibility criteria

Eligible women included those aged 30-45, ever married or sexually active, parous, currently non-pregnant, no menstrual regulation within the previous two weeks, and no cryotherapy within the previous six months. After the first few months of data collection, the age criteria were adjusted to include women through age 50 years.

Specimen and data collection

A questionnaire with basic demographic and clinical data was completed by the nurse before the physicians' examination. Before consulting the medical record, the physician completed the Pap smear and the visual inspection using 3% acetic acid and the Gynoscope. Results of Pap

smears and any subsequent colposcopy or histology were added to the records as they became available before data entry on the computer. Patients were to be seen by one of two physicians who were originally trained by the medical consultant. The participating gynecologists also completed a questionnaire on the acceptability of the method.

Pap smear slides were sent for analysis to YKI's PDD laboratory, and the visual screening results were recorded separately from the Pap smear lab results. Positive cases, which were defined as "moderate/severe dysplasia" (CIN II-III), based on visual and/or Pap screening were confirmed with a colposcopy/biopsy at YKI. Photographs of the cervix were to be taken at the time of the colposcopy. Women needing treatment were referred to PDD, RS Cipto Hospital, or a private facility. A subsample of women diagnosed with "normal" cervices were to be photographed as well. A random sample of 5% of each class of slides were to be sent to the University of Washington pathology laboratory for confirmation. Subsequently, however, the YKI pathology lab decided not to have outside review of their slides.

Data processing and analysis

All data were reviewed and entered into the computer under the supervision of the YKB statistician, using an EpiInfo data entry template. Analysis was carried out using SPSS/PC+. The first objective was to assess the accuracy of visual screening using the Gynoscope as compared to Pap smears in identifying a normal cervix, mild dysplasia, moderate to severe dysplasia (e.g., treatable, precancerous lesions), and suspected carcinoma in situ or invasive cancer. These results are based on a comparison of the clinical and laboratory results with the "gold standard" established as a combination of histology and cytology. Assessment of the acceptability (ease of use in terms of logistical and operational factors) of the device to clinicians was based on the clinician questionnaire. These results will be important in determining how to increase acceptability among clinicians, as their support of the method is crucial to its implementation and widespread use.

Preliminary results of Phase I

Among the first 808 women enrolled in the study, there were eight with a Pap result of CIN III or cancer. Nearly 60% of the women were 30-39 years old, with 28% aged 40-44 and the remaining 16% aged 45-50. Of those who were asked about earlier Pap smears (not done in the early part of the study), about 50% reported having had a previous Pap smear. A visual inspection of "moderate or severe aceto-white tissue" correctly identified seven of the eight women with a Pap result of CIN III or cancer (sensitivity = 87.5%), while only three women out of 800 were incorrectly classified as positive (specificity = 99.6%). If the visual inspection result of "any aceto-white tissue" were used, the sensitivity increased to 100% compared to Pap while the specificity declined to 96%. As the remainder of the data become available, it will be possible to see if these results hold up.

During the clinical training sessions with the Gynoscope at both YKI and YKB, it became clear that an appropriate light source must be identified or developed to facilitate cervical inspection. Several possibilities were discussed, such as devising a method by which a small flashlight and strap could be worn around the clinician's head or a small battery-powered light could be attached to the speculum. Apparently, such devices currently exist in Indonesia and are used by outreach health workers. These and other light sources are being explored by PATH.

Phase II

This phase will be carried out by YKB using nurse-midwives from their clinics around Jakarta and from the affiliated network of private nurse-midwives. Using eligibility criteria identical to those of Phase I, YKB will enroll women until at least 50 positive cases (estimated 1200-1800 women) are identified. Specimen and data collection, processing, and analysis will be similar to Phase I.

The results of Phase II will determine the level of prior clinical training and/or background necessary to use the Gynoscope successfully. A comparison of gynecologists and nurse-midwives will be based on three factors:

- Time needed to train in Gynoscope use
- Post-test results
- Percent of cases correctly diagnosed with the Gynoscope

Finally, the information will help determine the appropriate type and amount of Gynoscopic training that is required to use the device successfully and the appropriateness of two potential types of sites for aided visual inspection.

Final analysis of the Phase I data should be complete by late June 1994, while it is anticipated that Phase II will be completed in early 1995. Simplified screening techniques, accompanied by low-cost early treatment of dysplasia has the potential to drastically reduce the incidence of cervical cancer. And, based on the preliminary results, this study should provide useful insights into the feasibility of this strategy.◆

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11. Study Design Issues
Lynne Gaffikin, DrPH

Given that currently available means of cervical cancer screening may be impractical or unfeasible on a large scale in the developing world, it would appear worthwhile to more carefully consider the need for a study to investigate the relative usefulness of alternative screening methods.

The general hypothesis under consideration for such a study could be:

- whether visualization is equally as "effective" as the Pap smear (the current standard in many countries) as a screening technique for detecting abnormal cervices in developing world settings.

Assuming for hypothesis-testing purposes a one-sided test, the specific null hypothesis can be stated as follows:

- H_o: Pap smears are more sensitive, more specific and more "useful" than visual screening in detecting abnormal cervices.

Within the context of this study, "useful" can be defined in terms of predictive value positive (PVP) and negative (PVN), both of which are related to the prevalence of disease in the

population. Levels of sensitivity and specificity considered of public health importance in such a study need to be defined, but options are within 20% and 10% of Pap smear results, respectively.

An important component of the study which may need to be studied more qualitatively than quantitatively is how practical the two approaches to cervical cancer screening given the study and service delivery setting(s). The study should be be designed to maximize **internal validity** (i.e., limiting biases that could render conclusions incorrect/invalid) and **external validity** (i.e., limiting biases that could render results non-generalizable to the larger population of interest). A set of questions are delineated below which need to be considered as part of designing a valid study. The questions are not organized in order of importance, conversely the responses to all should be considered before finalizing the study design.

1. What is the larger population to which the results can be generalized?

This could include just women in urban areas, women using FP health facilities, all women, or women in certain age groups. The answer has implications in terms of who is eligible for the study (and recruitment strategies) and where study sites are selected.

2. What is the estimated prevalence of "disease" in the target population?

This has implications for the sample size and the estimated length of the study (which has obvious cost and logistic implications).

3. How are we defining "disease?"

Are we including CIN II, III or do we want to include CIN I cases also? Where is the cut-off point for both Pap smears and visualization? This has implications for where the sites can be selected, sample size and length of the study.

4. Where in the natural history of disease do we want to/can we intervene with treatment (and can this be/is this standard across all potential study countries)?

This depends in part on how the question above is answered and the status of cervical cancer screening and treatment in potential study countries. The rationale for this question is that one should not introduce a screening technique that identifies cases of diseases if confirmation and some treatment for these cases cannot be provided by the system as it exists or has the potential to exist.

5. What is the accuracy of Pap smear as the "gold standard" in different study countries? (i.e., how truthful is "truth"?)

This has implications for the degree to which another measure of "truth" needs to be included and sample size implications. For example, if by using another measure of "truth" in a particular setting Pap smears are found to be only 50% sensitive, for visual screening to yield results within 20% of Pap smears (i.e., 20% of 50%), would mean that visualization would only need to be 40% sensitive. Is this the analysis of interest or are

we looking to establish the sensitivity of visualization at at least 65% assuming Pap smears are 80% sensitive.

6. Who is the target audience for the study results?

This has implications for the amount of difference in sensitivity/specificity considered "acceptable" or of medical/public health importance. Potential end users include: national health program officials; the donor community; the medical community-physicians, nurses, etc.; women's advocacy groups; or all of the above. If the potential target audience differs in their opinion as to what is an "acceptable" level of difference in sensitivity/specificity between the Pap smear and visualization, the most conservative (i.e., lowest) level should be used unless this is impractical in terms of the required sample size.

7. What is the availability and accuracy of colposcopy/biopsy services in-country?

Related to this, what is the the willingness of these qualified professional staff to participate in such a study? The amount of turnaround time needed to provide a diagnosis has implications for the number of staff/sites required. This, in turn affects the potential need for stratification in the analysis which affects the sample size and, thus, the duration/length of the study.

8. Who in-country does/should do visual screening?

Should this be nurses, nurse/midwives, any physician or Ob/Gyns only? This will depend upon the service delivery policies of the individual country and is critical in terms of assessing differences in how practical the two approaches are. The response to this has implications for the final list of research questions being investigated through the study (e.g., are differences between nurses and physicians being investigated?), the potential need to stratify in the analysis, and thus, sample size considerations.

9. What are the current methods for visual screening in-country?

Is acetic acid or iodine (Schillers test) being used and if so, with or without any magnification? How responsive will providers be to modifying the methods they are currently using to conform to a study standard?

10. What is the availability of screening supplies and the acceptability of the different screening methods by the medical community?

The latter can be considered an image issue in that if providers are already using certain screening methods, they may not be enthusiastic about investigating a method they consider less scientifically "advanced," even if the method might be more useful/practical given constraints in their service delivery system. The response to the former has implications in terms of which visual screening method is involved in testing the study hypothesis and the potential for standardization across all potential study countries.

11. What is the current treatment capacity for advanced cases?

This is an ethical issue in that the study will identify cancer cases that require treatment possibly in numbers much larger than usual if intensive recruitment of women for screening is involved. Treatment for precancerous lesions must be made available as part of the study and policies must be clear regarding treatment for cancer cases.

12. What is the feasibility of standardizing diagnoses and data collection?

This relates to the acceptability of having one standard measure of "truth" for the whole study (e.g., a cytopathologist who visits each study site and assesses all slides or sending slides to one central place, e.g., Johns Hopkins University). A related question is what are the systems currently being used for classifying disease? In some countries classes are used, in others CIN terminology is the standard. How willing are study country personnel to modify their disease classification systems (or is it necessary)?

13. When do we want/need the results by?

Is there a programmatically opportune time when it would useful to have the results? This has implications for the number of sites selected to achieve the required sample size. How should the findings be disseminated to best result in positive programmatic changes?

14. To what extent can/should we supplement the current availability of supplies?

Would this render the study findings less valid as the setting would then not really represent the "actual situation" in a country. This is an issue that affects the generalizability of the results and the ability of the study to answer the question of "how practical is the alternative screening technique?"

15. What is the Pap smear policy in-country?

Are smears done once every 1/2/5 years or once in a lifetime? If smears are done regularly (e.g., annually) on the study group, there is the possibility that some women would potentially be enrolled in the study more than once. This situation would dilute the study results.

16. What are the risks versus benefits of this study?

There is no known risk and one benefit is that there is immediate feedback on whether the patient may have cancer. A potential disadvantage or discomfort relates to the issue of false positives (from visualization) who end up undergoing more tests.

17. What are the patient consent procedures/requirements in potential study countries?

Do these need to be standardized or conform to an international standard? This has implications for how the services can be delivered in each country during the study.

18. What is the definition of "competency" for trained providers?

How best can we standardize this across study countries? This has implications for training.

19. What is the usual follow-up regimen?

How does this differ now by country? What will be included as part of the study and will this be standardized across study countries.◆

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12. Consensus on Study Design Issues

Paul D. Blumenthal, MD, MPH

1. What should be considered a medically acceptable target for this study?

Sensitivity - within 20% of Pap smears
Specificity - within 10% of Pap smears
Cost-effective - 1/3 the cost of Pap smears

2. How will disease be defined?

Visual	**Pap**
Mild	less than CIN III = negative
Moderate	CIN IV + = positive
Severe	

3. What is "truth"?

If we only use the Pap smear, the most negative consequence would be overestimating the sensitivity of visualization. Suggest to cross-validate all/a sample of smears.

4. Which providers should be trained in the study?

Nurse-midwife practitioners and physicians, if possible.

5. Which sites should be included?

Rural areas where there is likely to be a high volume of positive cases. This will necessitate an IEC campaign before the study begins in these areas. General clinics (versus specialized, e.g., STD clinics) should be sampled to render the results more generalizable to the general population of women at risk

6. Who should diagnose?

One to two trained competent colposcopists. They should colposcope the first 100 negative cases (the exact proportion to be decided upon) during the same visit and all positive cases from visual screening (plus bioposy where indicated)

7. Sample size

It is estimated that 100 positive cases per country will be needed, possibly more in some countries, depending upon the need for stratification in the analysis. The exact total sample size required will be determined by taking a number of important variables into consideration (e.g., nurses versus physicians; different study sites, etc.).

8. Who should be eligible?

Women aged 25-40; with any level of parity; include those with previous Pap smears (not important to test); menstruating women can be included (although care should be taken to take a good smear); Women who are (known to be) pregnant should not be included; post-partum women should wait six weeks to be screened; exclude those previously treated, if this can be determined.

9. What system of classification is used in potential study countries?

	Brazil	**Thailand**	**Kenya**	**Philippines**	**Haiti**
Classification System	Class I Comment inflam. mild moderate severe cancer	I II Atyp III/suspect Ca IV/strongly suspect for Ca V/cancer	I II-infert., atyp III IV Ca	See Thailand	See Thailand
Available Therapy for Mild/Moderate Lesions	Office cautery	Cryo/CO_2	NO_2	Cryo/NO_2	Cryo/CO_2
Written Consent	Pap: No Colp: No	Pap: No Colp: No	Pap: No Colp: No	Pap: No Colp: No	Pap: No Colp: No

10. How to standardize reporting?

All study cytopathologists should use a standardized reporting format which will be introudced as part of their training. The format will be agreed upon before the study begins.

11. What information should be collected? Among others:

a. Previous pelvic (if yes, date)
b. Contraceptive method being used
c. Existence of any genital tract infection (GTI) (money for treatment of GTIs should also be included in the budget)
d. Menses/LMP
e. Parity
f. Age
g. Results of each screening technique

12. Possible categorization scheme for the two screening techniques:

Visual	**Pap**
Normal	Normal
High-grade lesion (CIN or SIL)	High-grade lesion (CIN or SIL)
Cancer	Cancer

APPENDIX I

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APPENDIX II

WORKSHOP AGENDA

Wednesday, March 2, 1994

1:00pm **Introduction and Review of Schedule**

1:30pm **Overview of Cervical Cancer and Cervical Cancer Screening in Developing Countries**
Dr. Vivien Tsu

2:30pm **Cervical Cancer Screening: Role of Human Papillomavirus (HPV) Testing**
Dr. Robert Kurman

3:30pm **Discussion**

4:30pm **The Management of Abnormal Pap Smears**
Dr. Janet Rader

5:30pm **Review of Day One Proceedings**

Thursday, March 3, 1994

8:30am **Status of Cervical Cancer Screening in Selected Countries**

Thailand	*Dr. Kobchitt Limpaphayom*
Kenya	*Dr. H. C. Sanghvi*
Haiti	*Dr. Jean-Robert Brutus*
Brazil	*Dr. Silvia Bomfim-Hyppolito*

Discussion

10:30am **Alternatives to Pap Smears for Cervical Cancer Screening**
Dr. Paul D. Blumenthal

11:30am **Demonstration of Available Systems for LOCIS (Low-Power Optical Cervical Cancer Screening)**
Dr. Noel McIntosh

1:30pm **Designing a Study for LOCIS**

- **Review of PATH Project (Indonesia)**
  Dr. Vivien Tsu
- **Suggestions for a Multicenter LOCIS Project**
  Dr. Lynne Gaffikin

3:30pm **Group Work: Guidelines for Alternatives to the Pap Smear**
Dr. Noel McIntosh (Moderator)

4:30pm **Next Steps**
Dr. Paul D. Blumenthal

Friday, March 4, 1994

8:30am **Presentation and Discussion of "Next Steps" Recommendations**
Dr. Paul D. Blumenthal

9:30am **Group Work: Drafting a Multicenter LOCIS Project**
Dr. Paul D. Blumenthal

11:30am **Review of Workshop Proceedings**

APPENDIX III

REFERENCES

Overview of Cervical Cancer and Cervical Cancer Screening in Developing Countries
Vivien Tsu, PhD

1. "Cervical Cancer: Vaccine among best prospects for prevention," WHO Press Release, April 6, 1994.
2. Judson, FN.: "Interactions between human papillomavirus and human immunodeficiency virus infections." In: Munoz N et al., eds. *The Epidemiology of Human Papillomavirus and Cervical Cancer*. Lyon: International Agency for Research on Cancer, 1992, pp 199-207.
3. Kiviat NB, Criochlow CW, Kurman, RJ.: "Reassessment of the morphological continuum of cervical intra-epithelial lesions: Does it reflect different stages in the progression to cervical carcinoma?" In: Munoz, N et al., eds. *The Epidemiology of Human Papillomavirus and Cervical Cancer*. Lyon: International Agency for Research on Cancer, 1992, pp 59-66.
4. Meheus A.: "Women's Health: Importance of reproductive tract infections, pelvic inflammatory disease and cervical cancer. In: Germain, A. et al., eds. *Reproductive Tract Infections*. New York: Plenum Press, 1992, pp 61, 78-91.
5. Parkin, DM: "Screening for cervix cancer in developing countries." In: Miller, AB, et al., eds. *Cancer Screening*. Cambridge: University Press, 1991, pp 184-198.
6. Sherris, et. al,: "Cervical Cancer in Developing Countries: A Situation Analysis" PATH July 1993.
7. Singh, V., Sehgal, A., Luthra, UK.: "Screening for cervical cancer by direct inspection." *Brit Med J* 304:534-535, February 29, 1992.
8. World Health Organization. "Control of cancer of the cervix uteri." *Bulletin of the World Health Organization*. 64(4):607-618, 1986.

Cervical Cancer Screening: Role of the Human Papillomavirus
Robert Kurman, MD

1. The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses. Report of the 1991 Bethesda Workshop. *JAMA* 1992; 267:1892.
2. Christopherson WM: "Dysplasia, carcinoma in situ, and microinvasive carcinoma of the uterine cervix." *Hum. Pathol* 1977; 8:489-501.
3. Nasiell K, Nasiell M, Vaclavinkova V: "Behavior of moderate cervical dysplasia during long-term follow-up." *Obstet Gynecol* 1983; 61:609-14.
4. National Cancer Institute Workshop. The 1988 Bethesda System for Reporting Cervical/Vaginal Cytological Diagnoses. *JAMA* 1989; 262:931-3.
5. Richart RM, Barron, BA: "A follow-up study of patients with cervical dysplasia." *Am. J. Obstet/Gynecol*. 1969; 105:386-93.
6. Roger V, Nasiell M: "Behavior of mild cervical dysplasia during long-term follow-up." *Obstet Gynecol* 1986; 67:665-9.

Treatment of Preinvasive Cervical Lesions
Janet Rader, MD

1. Benedet, JL., Miller, DM., Nickerson, KG: "Results of conservative management of cervical intraepithelial neoplasia." *OB GYN* 1992; 79:105-110.
2. Berget, A., Andreasson, B., Bock, JE. et al.: "Outpatient treatment of cervical intraepithelial neoplasia." *ACTA Obstet Gynecol Scand* 1987; 66:531-536.
3. Bigrigg, MA., Codling, BW., Pearson, P. et al.: "Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit." *Lancet* 1990; 336:229-231.
4. Bryson, SCP., Lenehan, P., Lickrish, GM.: "The treatment of grade III cervical intraepithelial neoplasia with cryotherapy: An 11-year experience." *Am J Obstet Gynecol* 1985; 151:201-206.

5. Ferenczy, A.: "Comparison of cryotherapy and carbon dioxide laser therapy for cervical intraepithelial neoplasia." *OB GYN* 1985; 66:793-
6. Gordon, HK. and Duncan, ID.: "Effective destruction of cervical intra epithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years experience." *Br J Ob GYN* 1991; 98:14-20.
7. Gunaskera, PC., Phipps, JH., Lewis, BV.: "Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in treatment of CIN, a superior mode of treatment." *Br J OB GYN* 1990; 97:495-
8. Jordan, JA., Woodman, CBJ., Mylotte, MJ., et al.: "The treatment of cervical intraepithelial neoplasia by laser vaporization." *Br J OB GYN* 1985; 92:394-398.
9. Keijser, KGG., Kenemans, P., van der Zanden, PHTH., et al.: "Diathermy loop excision in themanagement of cervical intraepithelial neoplasia: Diagnosis and treatment in one procedure." *Am J Obstet Gynecol* 1992; 166:1281-1287.
10. Kwikkel, HJ., Helmerhorst, TJH., Bezemer, PD.: "Laser or cryotherapy for cervical intraepithelial neoplasia: A randomized study to compare efficacy and side effects." *Gyn Oncol* 1985; 22:23-31.
11. Loobuyck, HA. and Duncan, ID: "Destruction of CIN I and II with the Semm cold coagulator: 13 years experience with a see-and-treat policy." *Br J OB GYN* 1993; 100:465-468.
12. Luesley, DM., Cullimore, J., Redman, CWE. et al.: "Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears." *Br Med J* 1990; 300:1690-1693.
13. Paraskevaidis, E., Jandial, L., Mann, EM., et al.: "Pattern of failure following laser for cervical intraepithelial neoplasia: Implications for followup protocol." *OB GYN* 1991; 78(1):80-83.
14. Prendiville, W., Cullimore, J., Normal, S.: "Large loop excision ofthe transformation zone (LLETZ): A new method of management for women with cervical intraepithelial neoplasia." *Br J OB GYN* 1989; 96:1054-1060.
15. Schantz, A. and Thormann, L.: "Cryosurgery for dysplasia of the uterine ectocervix." *ACTA Obstet Gynecol Scand* 1984; 63:417-420.
16. Townsend, DE., Richart, RM.: "Cryotherapy and carbon dioxide laser management of cervical intraepithelial neoplasia: A controlled comparison." *OB GYN* 1983; 61:73-.
17. Whiteley, PF., Olah, KS.: "Treatment of cervical intraepithelial neoplasia: Experience with the low-voltage diathermy loop." *Am J Obstet Gynecol* 1990; 162:1272-1277.
18. Wright, TC., Gagnon, S., Ruchert, et al.: "Treatment of cervical intraepithelial neoplasia using the loop electrosurgical excision procedure." *Obstet Gynecol* 1992; 79:173-178.

Cervical Cancer Screening in Haiti
Jean-Robert Brutus, MD, MPH

1. Fruchter, R. G.; Rémy, J. C.; Burnett,W. S.: Boyce, J. G.; "Cervical Cancer in Immigrant Caribbean Women." *AJPH*, July 1986, Vol. 76, #7
2. Mitacek E.J., St. Vallières and Polednak, A.P.: "Cancer in Haiti: 1979 - 1984." Distribution of various forms of cancer according to geographic area and sex. *Int J Cancer*, July 15, 1986.
3. Mondestin; Boisrond, J.; Cornely, JR; Joseph, J.: "University Hospital, 474 Pap Smears" 20.7% suspect Class III Malignancy C. 1987.
4. Nerette, Lionel: 1984
5. Péan, V.; Michel, J. B.: "Processus Tumoraux: Etude épidémiologique des tumeurs à l'Hôspital Albert Schweitzer." An epidemiological study of 20,000 specimens, 1956 to 1988.
6. Pitchenik, A.E.: Becker, D.M.; Hilsenbeck, S.G.;Trapido, E.J.; "Cancer among Haitians in Florida." *Cancer*, January 1, 1987.
7. Sherris, et. al.: "Cervical Cancer in Developing Countries: A Situation Analysis" PATH July 1993.

Methods of Cervical Screening
Paul D. Blumenthal, MD, MPH

1. Abrams, J.: "A Preliminary Study of the Gynoscope." *Am J Gynecol Health*. Vol IV. No. 1. pp. 37-43.
2. "Cervical Cytology: Evaluation and Mangement of Abnormalities." ACOG Technical Bulletin, No. 183, August 1993. Reprinted in *Int J Gynecol Obstet*, 1993, 43:212-220
3. Lonky, N.M., Edwards, G.: "Comparison of Chemiluminescent Light Versus Incandescent Light in the Visualization of Acetowhite Epithelium." *Am J Gynecol Health*. Vol. VI, No. 1. January/February 1992. pp. 11-15.

4. Olatunbosum, O.A., Okonofua, F.E., and Ayangade, S.O.: "Outcome of Cryosurgery for Cervical Intraepithelial Neoplasia in a Developing Country." *Int J Gynecol Obstet* 1992. 38:305-310.
5. Ottaviano, M., La Torre, P.: "Examination of the Cervix with the Naked Eye Using Acetic Acid Test." *Am J Obstet Gynecol* May 1982; pp. 139-142.