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Testing the naked eye observation of the cervix after application of acetic acid as an effective screening test for cervical dysplasia

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TESTING THE NAKED EYE OBSERVATION OF THE CERVIX AFTER APPLICATION OF ACETIC ACID AS AN EFFECTIVE SCREENING TEST FOR CERVICAL DYSPLASIA

by

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ABSTRACT

The Papanicolaou test is the recommended screening for cervical cancer. It has a high false-negative rate. Because of the imperfection of the Papanicolaou other screening tests have been developed. Five studies compared various aspects of different screening techniques with mixed results.

A quasi-experimental design study was constructed comparing the naked eye observation of the cervix to the colposcopy observation, and the naked eye observation of the cervix to the Papanicolaou test.

The sample of 136 women from the Las Vegas area, being seen at their regular clinics were examined with all three procedures. A physiologic framework directed this study. The research hypotheses included: 1) The naked eye observation of the cervix agrees with the colposcopy observation; 2) The naked eye observation of the cervix agrees with the Papanicolaou test; 3) The naked eye observation of the cervix increases detection of cervical dysplasia. Hypotheses 1 and 3 were accepted.

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CHAPTER I

INTRODUCTION

Problem

The Papanicolaou test (Pap) is generally accepted as the cytological standard for cervical cancer screening. It is commonly agreed that a yearly Pap will identify cancerous and precancerous lesions, thus reducing the morbidity and mortality associated with cervical cancer (Hocutt and Clark, 1992). The American Cancer Society recognizes the usefulness of the Pap as a screening tool and recommends the Pap for women who have reached the age of 18 or who are sexually active.

A major problem associated with the Papanicolaou test is its significant rate of error. False negative rates have been reported between a range of 6% to 55% (Figge, Bennington, & Schneid, 1970; Anderson, Flynn, Hickey, LeRiche, Matisic, & Saen, 1981; Morell, Taylor, Snyder, Ziel, Saltz, & Willie, 1982; Van der Graff & Vooijs, 1987; Yobs, Plot, & Hicklin, 1987). Human error has been identified as the main reason why this rate is so inconsistent and at times so high. Inadequate cervical sampling, incorrect use of sample fixative, inadequate staining of the sample and incorrect interpretation of the sample by the cytotechnologist, have all contributed to the rate of error (Figge et al., 1970; Anderson et al., 1981; Morell et al., 1982; Van der Graff & Vooijs., 1987; and Yobs et al., 1987). There is a need for a simple, inexpensive screening test that can be used in conjunction with the Pap which will detect additional cases of cervical disease not currently found by the Papanicolaou (Pap) test. Other techniques including,

cervicography, human papillomavirus deoxyribonucleic acid (DNA) detection, screening colposcopy and naked eye observation of the cervix after application of an acetic acid, have all been proposed as methods to augment the Pap and enhance the detection of cervical disease (Reid, Greenberg, & Lorincz, 1991; Spitzer, Krumholz, Chernys, Seltzer, & Lightman, 1987; Tawa, Forsythe, Cove, Saltz, Peters, & Watring, 1988). Of these the naked eye observation of the cervix is inexpensive, nonpainful, requires one to two minutes to accomplish and results are immediate. Because of the physical properties of cellular protein and acid, the application of acetic acid to the cervix permits visualization of abnormal cervical cells. Of all of the techniques that have been suggested to augment the Pap the acetic acid wash " is a safe, simple, and effective adjunct to the Papanicolaou smear for cervical cancer screening" (Slawson, Bennett, and Herman 1992, p. 274).

Colposcopy, which is the standard from which a definitive diagnoses is made, is magnification and visualization of the cervix after application of acetic acid. Confirmation of an abnormal Pap is done through a colposcopy directed biopsy. After applying acetic acid the practitioner looks through the colposcope at the cervix and is able to see the areas of cervical dysplasia. It is from these areas that the biopsies are taken.

Purpose

The purpose of this study was to test the validity of observation of the cervix after application of acetic acid as a technique to be used in conjunction with the Pap to decrease the false negative results seen with the Pap alone. In order to accomplish this the study had two parts. First, the study tested the validity of the naked eye observation of the cervix after application of acetic acid by comparing the results of the naked eye observation of the cervix with those of the colposcopy observation of the cervix. Next, this study examined the relationship of the results from the naked eye observation of the cervix and the Pap.

CHAPTER 2

LITERATURE REVIEW

Introduction

The first part of this chapter defines terms and procedures. It provides a background and context for the problem and current research related to the research question. The second part of this chapter describes current literature in the area of cervical screening.

Cervical cancer ranks sixth as a cause of cancer deaths in women (Garfinkle, 1991). In 1995, the American Cancer Society estimated there would be approximately 65,000 cases of cervical carcinoma in situ, 15,800 newly diagnosed cases, and 4,800 ensuing deaths (Wingo, Tong, & Bolden, 1995). Although the average age for cervical cancer is 52, there are many women in their 20s who are in a high risk category for cervical cancer (Beral and Booth, 1986; Maddux, Varia, Spann, Fowler, & Rosenmann, 1990).

In reviewing the literature on cervical dysplasia, there are numerous topics that must be understood before the significance of the Papanicolaou test, the acetic acid screening test, or the colposcopy exam can have meaning. Some of the areas include: (a) physiology of the normal and abnormal cervix, (b) cervical dysplasia and how it develops, (c) how cervical cancer is staged, (d) descriptions of the Pap test, (e) naked eye observation of the cervix after application of acetic acid, and (f) colposcopy examination.

Physiology

Normal Physiology

According to Hacker and Moore (1992) the squamous epithelial and columnar epithelial cells are the two types of cells in the vaginal and cervical area. During early embryonic development the upper vagina and the cervix are covered with columnar epithelial cells, later in intrauterine development, the columnar epithelium of the upper vagina is replaced by squamous epithelial cells. The columnar epithelial cells move toward the cervix, and upon birth, the columnar epithelial cells are limited to the endocervix and the central portion of the ectocervix. When menarche begins estrogen levels rise, causing the colonization of the vagina by Lactobacillus and a subsequent drop in vaginal pH, indicating an acetic condition (Hatcher, Trussell, Stewart, Stewart, Kowal, Guest, Cates, and Policar, 1994). During exposure to this acetic vaginal environment the columnar epithelium is replaced by the squamous epithelium in a process referred to as squamous metaplasia. This gives the columnar epithelium the appearance of retreating closer to the external os and finally into the endocervix.

In young adult women the squamous epithelium covers the vagina and the outside of the cervix. The columnar epithelium covers the endocervical canal and the area immediately around the external cervical opening or os. The junction between the columnar epithelium and the squamous epithelium at birth is called the original squamocolumnar junction. Throughout life, but particularly during adolescence and the first pregnancy, the columnar epithelium is covered by a metaplastic squamous epithelium. The area where the columnar epithelium meets the squamous epithelium later in life is called the new squamocolumnar junction. The area of metaplastic squamous epithelium that is between the original squamocolumnar junction and the new squamocolumnar junction is called the transformation zone.

Because the columnar epithelium is only one layer thick and underlying blood

vessels are visible, it appears red and almost grape-like. The squamous epithelium, which is more than one layer thick, does not allow the underlying blood vessels to show through. Hence, the squamous epithelium does not appear red (see Figure 1). In contrast, "the immature metaplastic cell is uniquely vulnerable to events that can modify the DNA of the cells nucleus, consequently developing into a premalignant or frankly malignant cervical lesion" (Hatcher et al.,1994, pp. 514-515). Therefore the area in which the immature squamous metaplasia is located, the transformation zone, is an area of active change and is the target area (Hacker and Moore, 1992).

Abnormal Physiology

Cervical Dysplasia. According to Hacker and Moore (1995), dysplasia is an abnormality in the shape, size and development of cells. Dysplasia refers to a pre-cancerous state. Dysplasia and lesion are two terms which are used interchangeably. The number of cells and the depth to which the lesion or dysplasia penetrates the squamous epithelial layer within the transformation zone determines the degree of dysplasia. Dysplasia can be from mild or low grade to severe or high grade while still being considered pre-cancerous. Because dysplasia is a pre-cancerous state not all dysplasia evolves into cancer. Some mild dysplasia will revert to normal cellular appearance and function spontaneously. Other dysplasia may take six to ten years to become a high grade lesion. In this study dysplasia is specific to the transformation zone of the cervix.

The squamous metaplasia process is a normal physiologic process by which the columnar epithelium is replaced by squamous epithelium. However under the influence of a carcinogen these normal changes take on an atypical appearance which results in an atypical transformation zone. Although it is not known why some women develop cervical lesions while others do not, some risk factors which have been identified

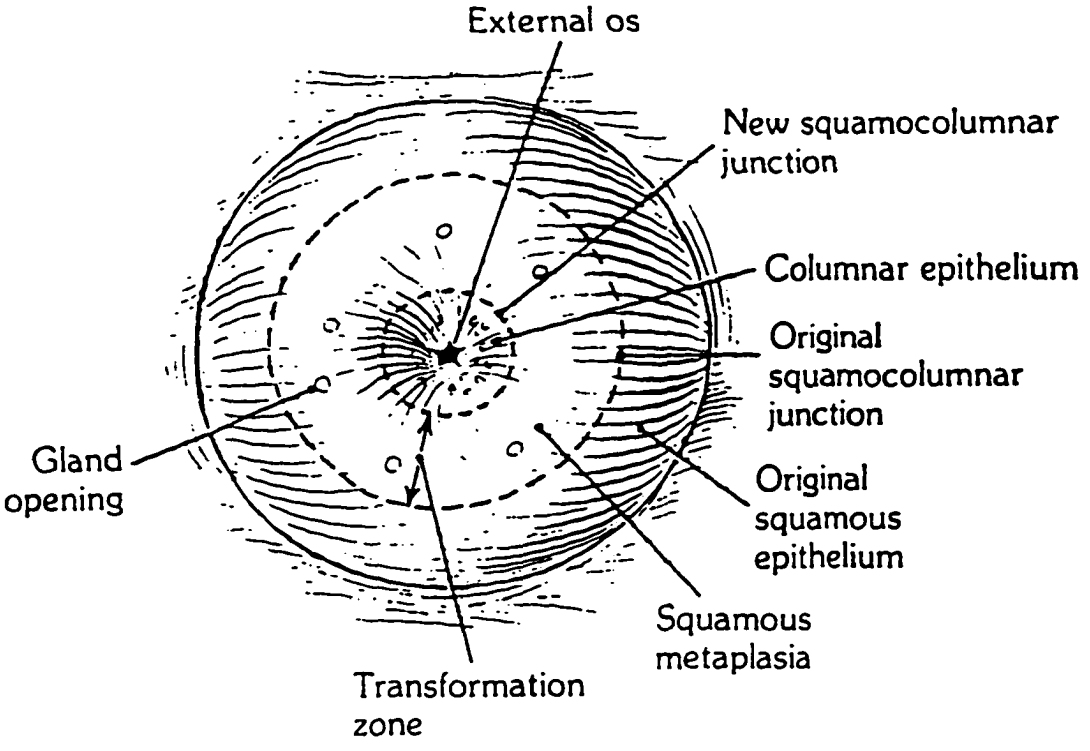

Figure 1. Illustration of the Cervix. (Hacker, N.F., & Moore, J.G. (1992). Essentials of obstetrics and gynecology. Philadelphia: W.B. Saunders Company, 589. Permission to reprint received from Saunders Publishing Co.)

include: (a) exposure to the Human Papilloma Virus (HPV) 16, 18, 31 and 33, (b) genetic disposition, (c) cigarette smoking, (d) more than three sexual partners, and (e) sexual activity before the age of 19 (Hacker & Moore, 1995).

Staging. Cervical lesions are rated or graded with a method known as staging. The gradation spectrum ranges from normal through invasive cancer. Currently, abnormal cytological findings on the Pap are reported according to the Bethesda System.

Originally the Pap smear reporting system, constructed in 1942 by Papanicolaou and Traut, was designed to diagnose cervical and uterine cancer. Any premalignant squamous epithelial changes were classified as dysplasia. Three levels of dysplasia identified were mild, moderate and severe. Any cervical cancer was classified as carcinoma-in-situ. Dysplasia was considered of lesser importance and was treated less aggressively than carcinoma-in-situ (Hatcher et al., 1994).

In the 1970s, this terminology was replaced with the term cervical intraepithelial neoplasia (CIN). CIN I was equivalent to mild dysplasia, CIN II to moderate dysplasia and CIN III to severe dysplasia and carcinoma-in-situ. This reclassification stressed that a premalignant lesion represented a process toward malignancy and that any CIN was on a continuum and needed to be treated before invasive cancer ensued (Hatcher et al., 1994).

The Bethesda Classification System, which is now the standard by which cytology is reported, abandoned the CIN classification system and provides a narrative descriptive diagnosis. This description allows for more information concerning the pathophysiology of the premalignant lesion. The system provides for descriptions of the cells in four categories: (a) infection, (b) reactive and reparative changes, (c) squamous cell abnormalities, and (d) gland cell abnormalities (see Tables 1 and 2). The readings of most concern are: (a) atypical squamous cells of undetermined significance (ASCUS),

Table 1

Bethesda System Reporting Categories

CATEGORY	READING
	Fungus
Normal with Infection	Trichomonas vaginalis
	Predominance of coccobacilli consistent with a shift in vaginal flora
	Bacteria morphologically consistent with Actinomyces sp.
	Cellular changes associated with herpes simplex virus
Normal with Reactive and Reparative Changes	Cellular changes associated with inflammation
	Atrophy with inflammation
	Miscellaneous: radiation, IUD, DES
Abnormal with Squamous Cell Abnormalities	Atypical squamous cells of undetermined significance (ASCUS)
	Low grade intraepithelial lesion (LGSIL)
	High grade intraepithelial lesion (HGSIL)
	Squamous cell cancer
Abnormal with Gland Cell Abnormalities	Endometrial cells, cytologically benign in a post-menopausal woman
	Atypical glandular cells of undetermined significance(AGUS)
	Adenocarcinoma

Adapted from Hatcher et al. (1994) Contraceptive technology. New York: Irvington Publishers, Inc., p. 521.

Table 2

Bethesda Cervical Rating System

Rating	Reading
Normal	None
Benign	Infection
	Inflammation
Epithelial Cell Abnormalities	AGUS
	ASCUS
	LGSIL
	HGSIL
	Cancer-in-situ
	Invasive Cancer

Legend

AGUS - atypical glandular cells of unknown significance

ASCUS - atypical squamous cells of unknown significance

LGSIL - low-grade squamous intraepithelial lesion

HGSIL - High-grade squamous intraepithelial lesion

Adapted from Shingleton H.M., Roman, P.L., Johnston, W.W., & Smith R.A. (1995). The current status of the Papanicolaou smear. CA A Cancer Journal for Clinicians, 45(5), 308.

(b) glandular cells of undetermined significance (AGUS), (c) low grade squamous intraepithelial lesions (LGSIL) and (d) high grade squamous intraepithelial lesions (HGSIL). ASCUS and AGUS represent cellular changes that cannot be attributed to inflammation or a reparative process. However, the cellular changes are not consistent with either low grade or high grade intraepithelial lesions. The Bethesda System also incorporates an evaluation of the specimen adequacy as part of the report. If no squamous epithelial cells are seen in the specimen that is noted in the report. A Pap without squamous epithelial cells is considered inadequate and no reading can be obtained (Hacker & Moore, 1995).

An area designated as normal range which is of particular interest is the area of reactive and reparative changes. According to Frisch (1987), inflammation which is part of this category represents 10% of all Pap results. It is within this area that the Pap may be missing a portion of dysplasia.

Tests

Naked Eye Observation of the Cervix

A mild acetic acid is applied to the cervix. The cervix is then viewed with the naked eye of the observer, without magnification. The squamous metaplasia cells that make up the transformation zone are identified first. They are normally pink and smooth. Because acetic acid causes abnormal cells to whiten, any area that appears white within the transformation zone is considered abnormal. If all areas appear pink within the transformation zone then the test is considered normal. This criteria is based on previous research standards of Ottaviano and La Torre (1982), Fiscor, Fuller, Jeromin, Beyer, and Janca (1990), Slawson et al. (1992), Van Le, Broekhuizen, Janzer-Steele, Behar, and Samter (1993), and Frisch, Milner, and Ferris (1994).

Colposcopy

The colposcope was invented in 1925 by Hans Hinselmann (Giuntoli, Atkinson, Ernst, Rubin, and Egan, 1987). Because of negative publicity, it took more than 20 years for the technique to come from Germany to the United States. A colposcope is a device which uses a lens to magnify the cervix. Some colposcopes have monitors attached, allowing the patient to see their cervix during the examination. Colposcopes may also have a camera attached so that a still photograph of the cervix can be made.

Colposcopy is a procedure in which a mild acetic acid is applied to the cervix. Acidic acid causes dysplastic cells to whiten. The magnification of the cervix by the colposcope enhances visualization of the transformation zone and permits easier and more accurate identification of any aceto whitening. This enhancement also allows the practitioner to more accurately biopsy those areas which appear suspicious. However, colposcopy itself is nothing more than visualization of the cervix under magnification after an acetic acid wash has been applied (Hacker & Moore, 1995). Giuntoli et al. (1987) recommended that a woman have a colposcopy examination with biopsies for any of the following conditions: (a) persistent minimal dysplasia on recurrent Paps, (b) a major abnormality on one Pap, (c) a lesion seen by the naked eye in a routine gynecological exam or (d) exposure in utero to diethlstilbestrol (DES).

Papanicolaou Test

The Papanicolaou test, or Pap test, as it is commonly called, is a screening test for cervical abnormalities. It was introduced in 1928 by Papanicolaou (Koss, 1989). Laboratory examination of cells from the cervix can identify cancerous and precancerous lesions. The Pap is most reliable when the cells are taken from the transformation zone. This is because most cervical lesions arise from the squamous metaplasia cells in the transformation zone (Shingleton, Roman, Johnston, & Smith, 1995). Taking cells from

the surface of the transformation zone is accomplished in two ways for each Pap smear. The first is by inserting a small brush, called a cytobrush into the endocervix and rotating it 360 degrees. This effectively removes cells from the endocervix. The second method involves placing a small wooden or plastic spatula on the ectocervix and rotating it 360 degrees. This effectively removes cells from the ectocervix. Both procedures are used with each Pap test to ensure adequate sampling of the transformation zone (Shingleton et al., 1995). These cells are placed on a slide by the practitioner and a fixative is sprayed on them. This preserves the cells for later evaluation in the laboratory.

The Pap sampling is typically done in the practitioner's office without the aid of any other devices.

Research Related to the Screening Tests

There are only a few studies which address the use of the Pap in conjunction with another screening method. A review of this research is important to understand the current knowledge in this area and the current study design.

The first study to examine the use of screening techniques for cervical disease other than the Pap was done in Italy by Ottaviano and La Torre (1982). Two separate observations were made with two different observers. One researcher observed the cervix with the naked eye after application of acetic acid and a second researcher observed the same cervix with the colposcope after application of acetic acid. A 3% acetic acid wash was used in each observation to detect cervical changes. After applying the acetic acid wash and waiting one minute, the cervix was evaluated with the naked eye and with the colposcope. Of the 2,400 cases, 312 (13%) were identified as having abnormal cervices with both naked eye and the colposcope exams. Agreement between naked eye observation and colposcopy observation was 98.3%. Of these, 143 (46%) were found to have some type of dysplasia with biopsy and hystological exam. The other 54% had

normal biopsy readings. This study supports the position that naked eye observation and colposcopy observation are equivalent, and that almost half of the visual observations will not agree with biopsy and histology results. The authors suggested using naked eye observation of the cervix to supplement the Pap in early detection of cervical cancer.

Fiscor et al. (1990) used a sample of 145 women to compare three types of cervical screening. A 4% acetic acid wash was applied to the cervix and left on for 30 seconds before naked eye observation was done by one obstetric gynecological nurse practitioner. The nurse practitioner had had experience with over 300 naked eye observations before the study began. Other tests used in this study included the commercially available ViraPap and ViraType, nucleic acid tests for the detection of human papillomavirus (HPV), and the Pap.

Of the 145 cases, 36 (25%) were identified as abnormal by all methods. Naked eye observation following acetic acid wash identified 22 women (15%) as abnormal. The Pap alone detected cervical abnormalities in 6 women (4.3%). An additional 8 cases (5.5%) were both positive for naked eye with acetic acid and the Pap.

Because there was no confirmation of cervical disease with the use of a colposcopy or biopsy in this study, there was no way of knowing what percentage of these cases were actually normal. However, the authors concluded that the use of the HPV test and the acetic acid wash test are both useful in detecting cervical abnormalities that would not be found with the Pap alone. Of the acetic acid wash, they said, "Because the acetic acid test is inexpensive, we recommend that it be performed routinely." (p. 30)

A large study of 2827 women by Slawson, Bennett, and Herman (1992) used six clinical sites were used with an unspecified number of practitioners collecting the data. The practitioners were instructed about identification of abnormal cervices through the use of photographs.

The study examined the use of a 5% acetic acid wash in conjunction with the Pap.

Of the 2827 cases, a total of 358 (12.6%) were reported as abnormal by all methods. Only 63 cases (2.3%) of the total population was identified with cervical abnormalities using the naked eye observation after application of acetic acid alone. The Pap alone found 136 cases (4.8%). An additional 22 cases (1%) were found on the basis of a positive acetic acid and Pap. The remaining 4% were not followed up.

In this study biopsies were done to differentiate between normal and abnormal naked eye observation and the Pap. Of the 63 women who only had an abnormal acetic acid test, 30 (48%) had a normal biopsy. Of the 136 women who only had an abnormal Pap, 43 (32%) had a normal biopsy. Of the 22 women with both an abnormal Pap and abnormal naked eye observation, 8 (36%) had a normal biopsy.

Slawson et al. (1992) stated that detection of cervical disease was improved by 33% with the use of the acetic acid wash. The authors further suggested that the acetic acid wash be used to augment the Pap on routine screening visits for cervical abnormalities. Problems with this study included multiple examiners and educational preparation for performing the naked eye observation.

Van Le et al. (1993) studied 85 women all of whom had normal Pap tests and abnormal naked eye observations. Twenty clinical sites were used for data collection. An unspecified number of health care providers including nurse practitioners, physician assistants, and physicians, used a 4% acetic acid wash to make the initial naked eye observation. Educational preparation included didactic instruction and educational conferences. No practice preparation was involved. Colposcopy observation was done by two gynecologists with a 4% acetic acid wash.

Of these 85 cases the colposcopy observation agreed with the naked eye observation in 51 cases (60%) of the time. In those cases where naked eye observation and colposcopy observation agreed, biopsy confirmed dysplasia 41% of the time and

normal cervices 59% of the time.

This study did not support the naked eye observation and the colposcopy observation as equivalent. It recommended better educational preparation of the providers to refine their acetic acid interpretation. It did support previous data which shows approximately half of all abnormal naked eye observations or Paps are normal with biopsy.

A study released in 1996 by Megevand, Denny, DeHaeck, Soeters, and Bloch, questioned the use of the Pap, naked eye observation of the cervix after application of acetic acid, colposcopy observation, and biopsy in 2426 women. All Paps and naked eye observations were taken by one nurse who had received training for one week by an oncologist/gynecologist. There was no disclosure as to the type of training involved. A 5% acetic acid was applied to the cervix for one minute before the naked eye observation was taken. The colposcopy readings were done by an oncologist/gynecologist.

Agreement between the naked eye observation and the colposcopy observation was 2.5%. Of the 2426 cases, 330 (13.6%) were found to be abnormal using both methods. Fifteen cases (.04%) were identified with the naked eye observation alone. The Pap alone detected cervical abnormalities in 254 women (10.5%). An additional 61 (2.5%) were abnormal with both the naked eye observation and the Pap. Eighty-six percent had abnormal with biopsies, and 14% were normal with biopsy.

This study did not support the naked eye observation and the colposcopy observation as equivalent. Nor did it support other data that suggests approximately half of the abnormal Paps or naked eye observations will be normal with biopsy. In spite of this, the authors suggested the use of the naked eye observation of the cervix was a useful screening tool for cervical dysplasia in those areas where Pap screening was not available.

Other research which supports the use of the naked eye observation as a valid

screening test has been done. Frisch, Milner, and Ferris (1994) examined the use of the naked eye observation in conjunction with the Pap test and cervicography. Cervicography is a still photograph taken of the cervix after an acetic acid wash has been applied. Of the 95 cases seen, 40 had abnormal biopsy reports. Of these, 26 (65%) had a normal Pap test. The study demonstrated a normal Pap alone was 67% accurate in predicting a normal cervix. A normal acetic acid wash alone was 88% accurate in predicting a normal cervix. A normal Pap and normal acetic acid wash together were 91% accurate in predicting a normal cervix. This study showed the combination of these two tests increases the normal predictive value dramatically.

Inflammation which is classified as normal on the Bethesda System, has some interesting qualities, (Frisch 1987). Inflammation accounts for 10% of the Pap results. Based on a retrospective review of inflammatory atypia, Frisch found that 0.7% to 34% of inflammation results are likely to have some type of dysplasia using a 95% confidence interval.

Discrepant Results Related in the Literature

There are some discrepancies among the results of the various studies. Ottaviano and La Torre (1982) compared naked eye observation of the cervix after application of acetic acid and compared it to colposcopy. They reported a 98.3% agreement between the two results. However, the study by Van Le et al. (1993) only reported a 60% agreement between the naked eye observation and the colposcopy observation. Furthermore, Megevand et al. (1996) reported an agreement of only 2.5% when comparing naked eye observation of the cervix and colposcopy.

Evaluations of the accuracy of each user is equally divergent. When comparing the Pap and the naked eye observation of the cervix after application of acetic acid, Fiscor et al. (1990) found that 15% of abnormal results came from the naked eye

observation alone. A similar study by Slawson et al. (1992) showed that only 2.3% of all abnormal results came from the naked eye observation. Megevand et al. (1996) reported that .04% of abnormalities came from the naked eye observation alone. Therefore, results of these three studies are dramatically inconsistent.

When comparing naked eye observation to biopsy result, Ottaviano and La Torre (1982) found that 54% of the abnormal naked eye observations were normal. Slawson et al. (1992) found that 48% of the abnormal naked eye observations were normal. Van Le et al. (1993) found that 41% of the abnormal naked eye observations were normal. Megevand et al. (1996) found that 74% of the abnormal naked eye observations were normal. These results again demonstrate inconsistencies.

When comparing Pap observations with the biopsy results, Slawson et al. (1992) found that 32% of the abnormal Paps were normal on biopsy. However, Megevand et al. (1996) found that only 10% of abnormal Paps were normal.

Only the study by Fiscor et al. (1990) identified one data collector, a nurse practitioner who had 300 experiential readings before beginning observations in the study. All of the other studies either had multiple observers, or unspecified training, or both, raising the question of interrater reliability.

These studies each have design and/or methodological error which may have contributed to divergent findings. Multiple data collectors with variant educational training were used in several of the studies. Table 3 gives a summary of the design of the five key studies illustrating discrepancies in: (a) number of data collectors, (b) sample size, (c) education and (d) sites. Tables 4, 5 and 6 summarize the results of the key studies. These findings do not agree. These discrepancies must be looked at in light of the weakness of the designs.

Regardless of the discrepancies within this review of literature, each individual

Table 3

Summary of Key Study Designs

Study No.	Data Collectors	Sample Size	Education	Sites
1	2	2400	unknown	1
2	1	145	experience	multiple
3	multiple	2827	photos	6
4	multiple	85	books	20
5	2	2426	unknown	1

Legend

1 Ottaviano and La Torre (1982)

2 Fiscor et al. (1990)

3 Slawson et al. (1992)

4 Van Le et al. (1993)

5 Megevand et al. (1996)

Table 4

Summary Findings: Comparing Percent Agreement Between the Naked Eye and Colposcopy Results

Study No.	Percent NE = Colposcopy
1	98
2	NA
3	42
4	60
5	02

Legend

1 Ottaviano and La Torre (1982)

2 Fiscor et al. (1990)

3 Slawson et al. (1992)

4 Van Le et al. (1993)

5 Megevand et al. (1996)

NE = Naked Eye Observation

NA = Not Done

Table 5

Summary of Abnormal Results: Comparing Percents of Naked Eye, Pap, and Naked Eye + Pap

	Percent Abnormal			
Study No.	NE	Pap	NE + Pap	Total Percent
1	13	NA	NA	13
2	15	4	6	25
3	2	5	1	8
4	100	NA	NA	100
5	0.04	11	3	14

Legend

1 Ottaviano and La Torre (1982)

2 Fiscor et al. (1990)

3 Slawson et al. (1992)

4 Van Le et al. (1993)

5 Megevand et al. (1996)

NE = Naked Eye Observation

NA = Not Done

Table 6

Summary of Biopsy Results:Comparing Percents of Naked Eye, Pap, and Naked Eye + Pap

	Percent					
Study No.	NE		Pap		NE + Pap	
	normal	abnormal	normal	abnormal	normal	abnormal
1	54	46	NA	NA	NA	NA
2	NA	NA	NA	NA	NA	NA
3	48	52	32	68	36	64
4	41	59	NA	NA	NA	NA
5	74	26	10	90	16	18

Legend

1 Ottaviano and La Torre (1982)

2 Fiscor et al. (1990)

3 Slawson et al. (1992)

4 Van Le et al. (1993)

5 Megevand et al. (1996)

NE = Naked Eye Observation

NA = Not Done

research study has suggested using other types of screening methods. Specifically, they have suggested the naked eye observation of the cervix after application of acetic acid.

Summary

This chapter has defined some terms and screening tests including, normal physiology of the cervix, abnormal physiology of the cervix, past and present staging of cervical dysplasia, naked eye observation of the cervix after application of acetic acid, colposcopy, and the Pap test. It has also reviewed studies which have used the Pap in conjunction with other screening methods looking specifically at the relationship between the different methods. Reporetd results are inconsistent. According to current literature it is apparent that a Pap test alone is not an adequate screening tool for the detection of cervical disease. The studies by Ottaviano and La Torre (1982); Fiscor et al. (1990); Slawson et al. (1992); Van Le et al.(1993); Frisch et al. (1994); and Megevand et al. (1996); all recommend adding the acetic acid wash test as an augmentation to the Pap test. This test is inexpensive, noninvasive, nonpainful, and easily accomplished in the practitioner's office. Due to the discrepencies in the findings the following study was done controlling for design problems in the above studies.

CHAPTER 3

CONCEPTUAL FRAMEWORK

Introduction

This chapter examines the physiology of the normal and dysplastic cervical cell and explains the use of aceto white in identification of dysplasia to enhance diagnosis of cervical abnormalities. From this framework, the hypotheses, variables, and assumptions were developed.

Cellular Physiology

The normal cell has twenty-three pairs of chromosomes. It is in a haploid state, that is chromosomes occur as pairs. The abnormal or dysplastic cell does not have twenty three pairs of chromosomes, so it is not in a haploid state. Rather, the dysplastic cell has an odd number of chromosomes and pairs, referred to as chromosomal aneuploidy. Because of chromosomal aneuploidy, the abnormal cell has a greater nuclear to cytoplasmic ratio than a normal cell. This difference in nuclear material is the basis for the use of acetic acid test.

The acetic acid solution changes the cervical cell in two significant ways. First, it dissolves mucus on the outside of the cervix which allows for a clean and unobstructed view of the cervix. Next, it causes transient changes in the epithelial surface of the cervix by temporarily inducing intracellular dehydration and coagulation of protein. Because abnormal cells have more protein, they clump together and occlude the underlying

stromal vasculature, giving the abnormal cells an easily identifiable white or opaque appearance. Within a few minutes, the abnormal cells revert back to their original color. Normal cells with the correct amount of chromosomal and nuclear material do not coagulate, hence they do not occlude the underlying vasculature and they retain their pink color (Giuntoli et al.1987).

Giuntoli et al. (1987) recommends the application of a 1% to 5% solution of acetic acid for acetic acid testing; most often a 3% solution is used. The acetic wash is reportedly well tolerated by patients and produces the desired result in 1 to 2 minutes.

Research Hypotheses

Three research hypotheses are generated for this study.

1. The naked eye observational reading of the cervix after application of acetic acid will agree with the colposcopy observational reading of the cervix.
2. The naked eye observational reading of the cervix after application of acetic acid will agree with the Papanicolaou test result.
3. The naked eye observational reading of the cervix after application of acetic acid will increase detection of cervical dysplasia over that already detected by the Papanicolaou test.

Definitions

The independent variables were the three screening procedures: (a) naked eye observation of the cervix after application of acetic acid, (b) colposcopy and (c) Pap.

Naked Eye Observation

The observation of the cervix after application of a 5% vinegar solution and a one minute waiting period. The observational reading was normal (negative) if no aceto white was seen or abnormal (positive) if aceto white was seen.

Colposcopy Observation

The observation of the cervix after application of a 5% vinegar solution through the colposcope. The observation occurred after the naked eye observation. The observational reading was normal (negative) if no aceto white was seen or abnormal (positive) if aceto white was seen.

Papanicolaou Test

The cytological evaluation of endocervical and ectocervical cells from the cervix. Results received from Associated Pathologists Laboratories were reported according to the Bethesda classification system. Normal readings included inflammation and benign cellular changes. Abnormal readings included: (a) ASCUS (atypical squamous cells of unknown significance), (b) AGUS (atypical glandular cells of unknown significance), (c) LGSIL (low grade squamous intraepithelial lesion) and (d) HGSIL (high grade squamous intraepithelial lesion).

CHAPTER 4

METHODOLOGY AND PROCEDURES

In this chapter research design, sample, setting, measurement methods, procedure, ethical considerations and methodological limitations are discussed.

Research Design

A quasi-experimental design was used for this study. The treatment included acetic acid application to the cervix, with naked eye and colposcopy readings, and the Pap for all subjects. The dependent variables were the results of each of the three procedures.

Sample

The target population is all women who have reached menarche, are pre-menopausal, and sexually active. Convenience sampling of pre-menopausal sexually active multiparous or nulliparous women, fourteen years or older was done. Sampling took place from December 1996 through February 1997. Menopausal or post-menopausal women were excluded, because of the difficulty in visualizing the complete transformation zone. In these women, the squamo-columnar junction is within the endocervix. In order to assure no menopausal women were in the study, women over the age of 48 were excluded. Women who had hysterectomies were also excluded as they no

longer have a cervix or a transformation zone.

According to Burns and Grove (1993), in order to have a power level of .80, an alpha of .05, with a small effect size of .22, 136 women were needed to adequately test the hypotheses. The participants were chosen from women in the Las Vegas area who presented at their designated local clinics for their annual Pap screening test or follow up for dysplasia.

Setting

Three area sites were chosen to collect data. Two of the sites had a dysplasia clinic as well as normal gynecology clinics. Written approval was granted from the clinics (see Appendix E).

The first site had a dysplasia clinic with a colposcopy room. The colposcope was attached to a camera and video screen. This allowed the researcher to take still photographs and the participant to view her cervix. Because the colposcope was not portable, all Paps and observations were done in that one room. Two nurse practitioners, both certified colposcopists, did the Paps and took independent observational readings. These separate observations were recorded.

The second site also had a dysplasia clinic but did not have either camera or video capabilities. At this site the colposcope was portable and was moved from room to room as needed. There were nine different rooms that were utilized at this site. Paps were done by one nurse practitioner, three physician assistants, and three physicians. One gynecologist was on site part-time, and his observations were recorded on all the Paps and procedures that he did.

The last site did not have a dysplasia clinic and had a portable colposcope, again without camera and video capabilities, which was moved as needed. There were two

rooms at this site. All Paps were done by one nurse practitioner. No second observations were recorded at this site.

The exam rooms at all of the sites contained standard exam tables with stirrups. At each site, the Paps were done by the participant's designated provider. Each clinic used different light sources for the Pap. One had colposcope light only, one had the light source in the handle of the speculum and the last used a high intensity lamp. Because of this, the naked eye observations of the cervix and colposcopy observations were done with the light source from the colposcope.

Measurement Methods

Observation, from the naked eye observation of the cervix and colposcopy viewing, and tissue sample evaluation from the Pap test were the primary forms of measurement.

Observation was the first form of measurement. Observation of the cervix was done in two ways. The first type of observation was performed with the naked eye. After application of a 5% the acetic acid solution and a waiting period of one minute, the cervix and the complete transformation zone were viewed. If there was no aceto white, the observation was graded as normal or negative for a lesion. Any aceto white observation was graded as abnormal or positive for a lesion. Any questionable areas not easily discernible were considered abnormal.

The second type of observation employed a colposcope. Two types of colposcopes were used. Each had their own light source attached and each was capable of 200x magnification. The two brands were Coopersurgical and Liesengang. Any observation which showed no aceto white was graded as normal or negative for a lesion. Any observation which showed aceto white was graded abnormal or positive for a lesion.

The second type of measurement was the Pap smear. The tissue samples were sent to Associated Pathologists Laboratories (APL), for standard cytological evaluation (see Appendix H). The standard procedure for evaluation of the Pap at APL includes readings by two separate cytotechnologists to decrease the rate of error. Results were reported to the clinic in its normal fashion according to the Bethesda classification system. The Bethesda classification system evaluates the adequacy and status of the sample. According to Shingleton et al. (1995) the sample must have endocervical and/or squamous metaplastic cells. These cells are found in the transformation zone. Any Bethesda rating of abnormality including: (a) ASCUS (atypical squamous cells of unknown significance), (b) AGUS (atypical glandular cells of unknown significance), (c) LGSIL (low-grade squamous intraepithelial lesion), (d) HPV (human papillomavirus), (e) HGSIL (high grade squamous intraepithelial lesion) and (f) invasive carcinoma was graded positive for a lesion (Shingleton et al., 1995). Any normal Pap was graded negative for a lesion (see Table 1).

Because this study was designed to test for the presence of dysplasia, not the degree to which it was present, the ordinal data from the Bethesda system records was interpreted and changed to reflect nominal data. Either the Pap was normal and the specimen was negative for a lesion, or it was abnormal and the specimen was positive for a lesion.

The data from the naked eye observation and the colposcope were both nominal. Either the observation was normal and the cervix was negative for a lesion, or the observation was abnormal and the cervix was positive for a lesion.

One researcher collected observational data. It was assumed that limiting data collection to one person would increase the reliability of the reading. The Pap was done by the participants normal provider, and the results were provided by APL.

Training for cervical observation consisted of 40 hours of observation of the cervix with the naked eye and with the colposcope both before and after application of acetic acid. This training included observation of approximately 50 patients. The training was under the direct supervision and tutelage of a certified colposcopist at one of the OB/GYN collection sites. To insure interrater reliability an additional 30 percent of the observational readings were repeated by three certified colposcopists intermittently through the data collection phase. Their observations were recorded and compared to the researchers observations. A second Pap was not necessary because the interpretation of the Pap was done through APL, not through the observer.

Procedure

Demographic Data Collection

The same room was used for the Pap, naked eye observation, and colposcopy. Pap, naked eye observation and colposcopy procedures were structured sequentially. As the woman was at the clinic for her scheduled Pap, it was done first. The naked eye observation of the cervix after application of acetic acid occurred next. This occurred before the colposcopy because the colposcopy is essentially the same test with magnification. The study was designed to test the efficacy of the naked eye observation as a screening tool, colposcopy could bias the observation of the naked eye because colposcopy should give a clearer view of the cervix due to its magnification.

Clients were scheduled by the clinics. The client, who met study criteria of (a) age, (b) pre-menopausal, (c) post menarche, (d) sexually active and (e) intact cervix, was asked by the researcher if she would participate in the study. The purpose of the study was explained to the participant before they signed the consent. A copy of the consent form was given to the participant. Before beginning the exam a demographic interview of the participant was done by the researcher. She was assigned an

identification number which was used to identify her results.

Pap Test

The participant was asked to undress from the waist down and sit on the examining table. Drapes were provided. The examiner left the room while the participant did this to provide privacy.

The participant was asked to lie in the lithotomy position with her feet in the stirrups. A speculum was inserted into the vagina, and the cervix was visualized. A wooden or plastic spatula was used to scrape cells from the vaginal wall. These cells were placed onto a glass slide. The rounded end of the spatula was used to scrape cells in a 360 degree turn from the transformation zone on the ectocervix. These cells were placed on the same slide. A cytobrush was inserted into the os, or endocervix, and rotated 360 degrees. These cells were placed on the same slide. A standard fixative, supplied by APL, was sprayed on the cells from a distance of eight to twelve inches. This completed the Pap.

Naked eye observation

With the patient in the same position and the speculum in the vagina, a standard 5% acetic acid solution was applied to the cervix with a large cotton swab or with a spray bottle. This was done until the cervix was adequately covered to remove secretions and to completely coat the transformation zone of the cervix. After one minute, the cervix was viewed and the transformation zone was identified. It was graded as either normal in appearance or abnormal. Any aceto white area inside of the transformation zone was considered abnormal.

Colposcopy

The colposcope was put into position to view the cervix. The cervix was viewed under magnification. Without re-application of acetic acid and using the same criteria as for the naked eye observation, the cervix was graded as either normal in appearance or abnormal. The speculum was removed, and the screening was finished.

The three steps to the procedure did not take more than five minutes. The naked eye observation data and the colposcopy observation data were recorded immediately after observation. The data from the Pap smear were recorded when the results are received from APL in three to seven days.

Ethical Considerations

Approval was received from the University of Nevada Las Vegas Department of Nursing Human Subject Rights Committee on December 6, 1996, and from the University of Nevada Las Vegas Biomedical Committee of the Institutional Review Board December 9, 1996 (see Appendix F). Study sites also gave written approval (see Appendix E).

All Pap results, as per the clinics' normal reporting procedure, were given to the participants. Individual results of the naked eye observation of the cervix and colposcopy were offered to each participant and placed in their chart for use by the primary care provider. Complete results of the study were made available on request to each participant. Because the Pap result was not known immediately, a number was assigned to each participant which corresponded to her name. The clinic was asked to provide the researcher with the result of the Pap.

There were no known risks to the women in this study. No risks were identified with the Pap test or the acetic acid application to the cervix. The study could benefit each

individual participant because there was potentially a greater chance of identifying cervical dysplasia. If cervical dysplasia is identified early, the medical procedures to complete a cure can be less emotionally and physically traumatic, and less costly to the woman.

Methodological Limitations

Observational bias with the colposcopy data was possible because one researcher made both the naked eye and colposcopy observations. The naked eye observation occurred first and it was possible that it biased the colposcopy observation. However, it also seems logical that what was seen with the naked eye would be more apparent with the colposcope. Sampling was non-random and from three convenience sites. This must be considered when interpreting the findings.

CHAPTER 5

RESULTS

This chapter presents the results of the study. The demographic data describing the sample precedes the hypotheses testing.

Demographics of the Sample

The sample consisted of 136 women. Of the 138 women asked to participate in the study, two declined. Of the 136 women in the study, 129 requested the summary results of the study. Tables 7-17 define the sample.

Most of the women in the study were between 20 and 39 years old (50.3%) (see Table 7). Approximately half of the participants had never smoked before, and the other half had either currently smoked or admitted to smoking in the past (see Table 8). Although one third of the women had never been pregnant the average pregnancy rate per person was approximately 1.5 times (see Table 9). Eighty percent of the women were using some type of birth control. The preferred birth control was an oral agent. About 20% of the sexually active participants were not using any type of protection (see Table 10). Of the 136 women, 82 (60%) had always had a normal Pap, while 40% had a history of some type of dysplasia (see Table 11). National data for smoking , pregnancy and type of birth control are consistent with the sample percentages. Mean age of participants in this study was 27.3 years, while the national average for pre-menapausal women is 35.2

Table 7

Summary of the Age of the Participants

Age in Years	N	Percent
14-19	19	13.9
20-29	68	50.5
30-39	38	28.1
40-48	10	6.8
Missing	1	0.7
Total	136	100.0

Mean = 27.3 S.D. = 7.6

National Data, Women Ages, 1994 = 35.2 years

Table 8

Summary of Smoking History of Participants

Smoking	N	Percent
Non-Smoker	71	52.5
Smoker	36	26.8
Former Smoker	28	20.7
Missing	1	0.0
Total	136	100.0

National Data, Women Smokers 1994 = 24.6%

Table 9

Summary of Pregnancies of Participants

Pregnancy	N	Percent
0	46	33.8
1	34	25.0
2	24	17.6
3	15	11.0
4	6	4.4
5	2	1.5
6	2	1.5
9	2	1.5
Missing	5	3.7
Total	136	100.0

Mean = 1.5 S.D. = 1.7

National Data, Lifetime Births Expected 18-34 years = 2.09

Table 10

Summary of Birth Control Methods

Birth Control	N	Percent
Oral	64	47.0
DepoProvera	7	5.1
Condom	22	16.2
Tubal Ligation	9	6.6
None	25	18.4
Other	5	3.7
Missing	4	3.0
Total	136	100.0

National Data:
Oral = 47%
None = 24.2%
Condom = 16.2%

Table 11

Past Pap History

History	N	Percent
Normal	82	60.3
Abnormal	54	39.7
Total	136	100.0

years (U.S. Bureau of the Census, 1995). This suggests the participants are similar to the national population for these variables.

Ninety-two percent of the women had received a Pap within the past two years (see Table 12). Of those women who had delayed their Pap for three or more years, the average age was 34 years, and 73% of these women were current or former smokers. The number of participants from each site varied and the type of patient seen varied within the sites. At site A, 29 out of 37 women were being seen in the dysplasia clinic for follow up on previously abnormal Paps. At site B, 4 out of 43 patients were being seen for dysplasia. The third site C, which saw 10% more patients than either of the other two sites, did not have any dysplasia patients within the 56 participants (see Table 13).

Of the 36 women who currently smoked, 18 (50%) had a previous history of cervical dysplasia. Twenty-eight percent of former smokers had a history of cervical dysplasia compared to 37% of non-smokers. Inflammation data revealed that 22 of the cases had some type of inflammation. Forty-six percent of those who had inflammation on their Pap also had an abnormal naked eye observation (see Table 14). Results from those women who were being seen for dysplasia did not vary significantly from those being seen for their annual Pap (see Table 15).

Reliability Outcomes

Interrater agreement between the researcher and independent colposcopists was 87%. This was based on 46 or one third of the total sample size. Agreement between the researcher and the first and third colposcopists was 94.5% and 100% respectively. Agreement between the researcher and the second colposcopist was 74%. Of the five cases that were in disagreement four had Pap results that were consistent with the researcher's naked eye and colposcopy observation. The second colposcopist also had

Table 12

Summary of Year of Last Pap

Year	N	Percent
1979 -1994	11	8.0
1995 -1997	117	86.0
Missing Cases	8	6.0
Total	136	100.0

Mean = 95.5 S.D. =1.8

Table 13

Summary of the Number of Participants at the Three Data Collection Sites

Site	N	Percent
A	37	27.2
B	43	31.6
C	56	41.2
Missing	0	0.0
Total	136	100.0

Table 14

Inflammation Findings From the Normal and Abnormal Pap and Naked Eye

Type of Inflammation by Test Type	N	Percent
Inflam+ Pap-/Inflam- NE-	8	32
Inflam+ Pap-/Inflam- NE+	11	44
Inflam- Pap-/Inflam+ NE-	2	8
Inflam- Pap+/Inflam+ NE-	4	16
Total	25	100

Legend:

(NE-) normal naked eye observaion
(NE+) abnormal naked eye observation
(Pap-) normal Pap result
(Pap+) abnormal Pap result
(Inflam+) inflammation present
(Inflam-) inflammation not present

Table 15

Comparison of Naked Eye, Colposcopy and Pap Results of Patients From Dysplasia Clinic and Non-Dysplasia Clinic

Dysplasia Patients	Percent Agreement
NE with Colposcopy	100
NE with Pap	71

Non-Dysplasia Patients	Percent Agreement
NE with Colposcopy	98
NE with Pap	70

Legend:

NE = Naked Eye Observation

Table 16

Interrater Reliability Comparison of Researcher Observation to Independent Colposcopist Observation

Total Observation	N	Percent
Agreement	40	87
Disagreement	6	13
Total	46	100

r = 0.819 p = 0.000

two cases which were given a normal naked eye observational reading and an abnormal colposcopy observational reading (see Table 16).

Hypothesis Testing

Each of the three hypotheses are discussed separately.

Hypotheses 1. The naked eye observation of the cervix after application of acetic acid agrees with the colposcopy observation.

To determine the relationship between the naked eye observation and the colposcopy observation, crosstabs was run. A 98.5% agreement was found between the naked eye observational reading and the colposcopy observational reading. In two cases, the naked eye was unable to detect an aceto white which was detected with the colposcope. The Chi-Square Value was 125.53, with a significance of 0.000. The point estimate was 1.5%. These figures suggest that the naked eye observational reading of the cervix and the colposcopy observational reading of the cervix are in agreement and not occuring by chance. The point estimate of 1.5% suggests the clinical difference between the two tests is absent. Therefore, the null hypothesis is rejected, and the research hypothesis is accepted.

Table 17

Hypotheses 1: Summary of Naked Eye Observations and Colposcopy Observations

	Naked Eye	Colposcopy
Normal	103	101
Abnormal	33	35
Total	136	136

Agreement = 98.5%

Chi-Square = 125.53

Significance = 0.000

Point Estimate = 1.5%

Hypotheses 2. The naked eye observation of the cervix after application of acetic acid agrees with the Papanicolaou test.

To determine a relationship between the two variables, crosstabs was run. An abnormal naked eye observation agreed with an abnormal Pap 5.1% of the time. A normal naked eye observation agreed with a normal Pap 66.2% of the time. Overall, there was a 71.3% agreement between the naked eye observation and the Pap. The Chi-Square Value was 1.326, with a significance of 0.249. The point estimate was 42%. These figures suggest the agreement of the naked eye observational reading of the cervix and the Pap result are occuring by chance ($p < 0.05$). The point estimate of 42% suggests the difference between the two tests is clinically significant. Therefore, the null hypothesis is retained.

Table 18

Hypotheses 2: Summary of Agreement and Disagreement for Naked Eye Observation and Pap Results

Agreement between Naked Eye and Pap	N	Percent
Normal Naked Eye and Normal Pap	90	66
Abnormal Naked Eye and Abnormal Pap	7	5
Sub-Total	97	71

Disagreement between Naked Eye and Pap	N	Percent
Normal Naked Eye and Abnormal Pap	14	10
Abnormal Naked Eye and Normal Pap	25	18
Sub-Total	39	29
Grand Total	136	100

Chi-Square = 1.326

Significance = 0.249

Point Estimate = 42%

Hypotheses 3. The naked eye observation of the cervix after application of acetic acid increases detection of cervical dysplasia over that already detected by the Papanicolaou.

To determine the relationship between the naked eye observational reading alone and the Pap alone crosstabs was run between these two variables. Forty-six of the 136 samples (33%) showed some type of abnormality. An abnormal naked eye observation alone accounted for 25 (55%) of all abnormalities. An abnormal Pap alone accounted 14 (30%) of all abnormalities. An abnormal Pap and an abnormal naked eye accounted for 7 (15%) of all abnormalities. The Chi-Square Value was 136.0, with a signigicance of 0.000. The point estimate was 25%. These figures suggest that the naked eye observational reading of the cervix and the Pap are not in statistical agreement. The point estimate of 25% further suggests the difference between the two tests is clinically significant. Therefore, the null hypothesis is rejected, and the third research hypothesis is accepted.

Table 19

Acetic Acid Test Compared with the Pap Test

Abnormality	N	Percent
Pap Alone	14	30
Naked Eye Alone	25	55
Pap and Naked Eye	7	15
Total Abnormalities	46	100

Chi-Square = 136.0

Significance = 0.000

Point Estimate = 25%

CHAPTER 6

DISCUSSION

Intent and Format of Study

A problem with the current Papanicoloau screening test was supported in the literature review. Five studies from 1982-1996 discussed various aspects of the use of the naked eye observation of the cervix as a screening technique to augment the Pap. Finding a way to augment the Pap could result in earlier detection and treatment of cervical dysplasia, thus reducing the morbidity and mortality associated with cervical cancer.

This study was designed to determine if the naked eye observation of the cervix after application of acetic acid is a valid screening test for cervical dysplasia. In order to accomplish this, the study was divided into two parts.

The first part of the study compared the observational reading of the naked eye with the observational reading of the colposcope. This was designed to determine if a practitioner could accurately identify cervical abnormalities with their eye alone. Because colposcopy is the standard from which a definitive diagnoses is made, it was chosen as the standard to which the naked eye observation would be held. If results were consistent between the naked eye observational reading and the colposcope observational reading, then accurate identification of cervical dysplasia could be confirmed.

The second part of this study compared the observational reading with the naked eye to the Pap result. If the results were the same then there would be no reason to use the naked eye observation of the cervix as the Pap is the standard screening tool presently

used. If the results varied such that the naked eye observational reading increased the total number of abnormalities recorded then it could be considered a reliable screening tool that could be used to augment the Pap test.

Interpretation of the Results

Comparison of the Sample to the Population

The sample population of women was similiar to the national population of women in: (a) smoking habits, (b) birth control habits, (c) age, (d) and number of pregnancies. Other national data on Pap history and dysplasia was not available. These similarities between the sample and the target population offer some support to the extrapolation of the findings for the larger group.

Comparison of Findings with Previous Research

Research hypothesis one, naked eye observation of the cervix after application of acetic acid agrees with colposcopy observation, was accepted. Agreement between the two observations was 98.5%. In two cases with an abnormal colposcopy the naked eye observation was of a normal cervix. However upon further examination with the colposcope, which gives a magnified view, a small abnormal aceto white area was apparent in both.

The agreement between naked eye observation and colposcopy observation in this study was consistent with the 98.3% agreement seen by Ottaviano and La Torre (1982). It does not agree with the studies by Van Le et al.(1993) and Megevand et al.(1996), (see Table 4). The different percentages for agreement may have been due in part to the number of people making the observations and training procedures received by the observers. In the two studies with the greatest agreement between naked eye and colposcopy, only one or two researchers did all of the data collection. In the current

study, only one researcher did the data collection.

The colposcopy observation confirmed the naked eye observation. Because of this, further comparisons with the Pap were done with the data from the naked eye observation.

Naked eye observational readings agreed with the Pap result 71% of the time. The naked eye identified 29% more cases of dysplasia than the Pap alone. There was no statistical significance in these numbers, suggesting the naked eye observational reading and the Pap results are not the same. If the two tests had been in agreement, there would be no reason to use the naked eye observation as a screening tool to augment the Pap. Both tests would be picking up the same dysplasia. The point estimate was 42%, suggesting the difference between the two tests is of clinical importance.

Other studies revealed varied agreements. Slawson et al. (1992) found a 93% agreement between the naked eye observation and the Pap result. Megevand et al. (1996) found an 89% agreement and Fiscor et al. (1990) found an 80% agreement. As agreement between the naked eye observation and the Pap approaches 100%, the usefulness of the naked eye observation as a screening tool to augment the Pap declines.

Of the 136 observations in this study 46 (34%) had a cervical abnormality either through a positive aceto white or a positive Pap or both. This compares with the study by Fiscor et al. (1990) where 25% were found to be abnormal (see Table 4). Other studies showed lower abnormal rates, 13%, (Ottaviano & La Torre, 1982); 12.6%, (Slawson et al., 1992); 13.6%, (Megevand et al.,1996).

Looking only at positive naked eye observations this study identified 19% abnormal cervices. Fiscor et al. (1990) identified 15% cervices as abnormal. Ottaviano and La Torre (1982) identified 13% as abnormal. The studies by Megevand et al. (1996), and Slawson et al. (1992) identified only .04% and as 2% as abnormal (see Table 5).

The inability of these last two studies to identify naked eye abnormalities may be

due to problems already discussed, such as the number of people making observations or lack of expertise on the part of the observer. It was already noted that the agreement between naked eye observational readings and Pap results were very high, in the Megevand et al. (1996) and Slawson et al. (1992) studies, with 88% and 93% respectively. It would follow that with such high percentage agreements these studies would also reflect very low naked eye identification of abnormal cervices.

This study did not evaluate the abnormal observational readings with biopsies. By comparing the results from Ottaviano and La Torre (1982) and Van Le et al. (1993) to this study, it could be expected that approximately 45% or an additional 11 to12 women would have biopsy proven dysplasia based naked eye observation alone. This is a clinically significant number of women who would not have been identified if the Pap was used alone.

An area of concern which was not addressed in the studies is the area of inflammation. According to Frisch (1987) inflammation, which is considered a normal Pap result, may contain the false negative readings. Frisch (1987) maintained that 0.7% to 34% of false negative Pap readings were found within inflammation. In this study, 46% of those Paps with inflammation had abnormal acetic acid observations, and it is possible that the abnormal acetic acid observation was detecting an area of dysplasia that the Pap over looked.

Limitations of the Study

This study did not utilize biopsies to support dysplasia readings as it was cost prohibitive. It relied upon other studies which had similar percentages to infer biopsy results.

The convenience sample came from three sites, two of which had dysplasia clinics within them in one city. Because percentages did not vary significantly between

the patients with dysplasia and the patients seking annual Pap exams, it is suggested that the results from this study may be found regardless of the women's dysplasia history. Results do not apply to women who were excluded from the study including women who are not sexually active, have had hysterectomies, have not reached menarche, or who are menopausal or post-menopausal. National data concerning dysplasia history and frequency of Pap exam was not available for comparison. Because of the sampling technique and sample size extrapolation of the findings from this study should be done with caution.

Implications and Recommendations for Future Research

The results of this study indicate that the use of the naked eye observation of the cervix after application of acetic acid is an effective screening test for cervical dysplasia. However, because of the variance within the review of literature and this study and the concerns raised about adequate training, it is important that the practitioner using this screening tool is well versed in normal and dysplastic cervices. If not well prepared in performing this procedure, results are questionable and may lack reliability.

Additional studies need to identify the education needed to prepare practitioners in valid use of naked eye observation of the cervix for abnormalities. Replication studies need to be done to clarify the discrepancies that are currently apparent in the literature. These studies should include comparisons between the Pap test, naked eye observation of the cervix, colposcopy observation of the cervix and biopsy. Further study also needs to be done in the area of inflammation. Very little has been done in this area to identify whether inflammatory tissue is normal or dysplastic. Finally practitioners need to understand the value of the naked eye observation. Because naked eye observation picks up a significant number of women with dysplasia it needs to be incorporated in the

annual Pap screening procedure. Doing this inexpensive, minimally time consuming and painless test can save the lives of pre-menopausal women.

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UNLV
UNIVERSITY OF NEVADA LAS VEGAS

APPENDIX A

CONSENT FORM

I_____, agree to take part in this research study. I understand that Carol Schmidt RN, a graduate student in Nursing at the University of Nevada, Las Vegas, will conduct this research. I understand that this study is designed to look at changes on my cervix that can be seen with the naked eye after the application of a 3% acetic acid. Acetic acid is another name for household vinegar. The purpose of this study is to test this screening procedure which is designed to increase the chance of finding abnormal cells on my cervix.

I understand that after my routine Pap test a 3% acetic acid solution will be applied to my cervix. I may possibly feel a cool sensation, simply because the acetic acid is at room temperature. My cervix will be graded for abnormalities viewed with the naked eye. Any areas that appear white will be considered abnormal. Next my cervix will be viewed through a colposcope. I understand that the colposcope magnifies my cervix and makes changes easier to see. Again any areas that appear white will be considered abnormal. I understand that the acetic acid will not harm me in any way and that it is the standard solution used with colposcopy. The effects of the acetic acid last for 1-3 minutes. I understand that it will not take more than four minutes to complete this test. The results of the observations will be given to my health provider, and to me from my health provider. I will be notified of the results of the Pap smear in the usual way for this clinic.

Any questions I have will be answered. I reserve the right to choose not to participate at any time. I also understand that my name will not be used. I will be assigned a number which will identify the observational results with the Pap results. I will receive a copy of this consent form.

If I have any questions about the research I can contact Carol Schmidt RN, through the Nursing Department at UNLV, 895-3360. If I have questions about the rights of research subjects I can contact the Office of Sponsored Programs at UNLV, 895-1357.

_____	_____	_____
Signature	Witness	Date

Department of Nursing
4505 Maryland Parkway • Box 453018 • Las Vegas, Nevada 89154-3018
(702) 895-3360 • FAX (702) 895-4807

APPENDIX B

DEMOGRAPHIC DATA COLLECTION

ID #_____

Age_____

Smoking Status
- Non-Smoker_____
- Presently Smoker_____
- Former Smoker_____

Number of pregnancies_____

Type of birth control_____

History of abnormal Pap_____

Date of last Pap_____

APPENDIX C

HUMAN SUBJECTS RIGHTS

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

DATE: December 9, 1996

TO: Carol Schmidt (NUR)
M/S: 3018

FROM: Dr. Lawrence Golding
Chairman, Biomedical Committee of the
Institutional Review Board

RE: Status of Human Subject Protocol entitled:
"Is the Naked Eye Observation of the Cervix After Application of Acetic Acid an Effective Screening Test for Cervical Dysplasia?"

OSP #501s1296-143

This memorandum is official notification that the protocol for the project referenced above has been approved by the Biomedical Committee of the Institutional Review Board. This approval is approved for a period of one year from the date of this notification and work on the project may proceed.

Should the use of human subjects described in this protocol continue beyond a year from the date of this notification, it will be necessary to request an extension.

If you have any questions or require any assistance, please give us a call at 895-1357.

cc: Dr. M. Louis (NUR-3018)
OSP File

Office of Sponsored Programs
4505 Maryland Parkway • Box 451037 • Las Vegas, Nevada 89154-1037
(702) 895-1357 • FAX (702) 895-4242

DEPARTMENT OF NURSING

UNIVERSITY OF NEVADA, LAS VEGAS
4505 MARYLAND PARKWAY • LAS VEGAS, NEVADA 89154-3018 • (702) 739-3360

06 December 1996

Carol Schmidt, BSN, RN
1403 Bareback Ct
Henderson NV 89014

Las Vegas NV

Dear Ms. Schmidt:

The Department of Nursing Human Subjects Rights Committee met and approved your proposal "Effectiveness of naked eye observation of cervix after application of acetic acid for screening for cervical dysplasia" with the following changes.

1. Clarify that permission will be obtained before the participant is moved to the exam room.
2. Add sentence to the consent form: after I understand that it ... test. "This time will be slightly longer than your usual exam time."
3. Add to last sentence paragraph 2 'results of the Pap smear in the usual time and manner for this clinic.'
4. Add to demographics sheet (to clarify your data obtained):

Non-smoker ___
Present smoker ___ Amount _____
Former smoker ___ Amount _____
Date Stopped _____
Number of miscarriages or abortions _____
Type of birth control _____ if used
History of abnormal Pap ____ Yes ____ No
History of STDs ____ Yes ____ No
Date of last Pap _____

When you have made the above changes you may take your proposal to the University Office of Sponsored Programs for their consideration. Please provide the Department of Nursing committee with a copy of the revised material.

You have a study that should result in useful information for nursing. The Committee wishes you well in completing it. If any of the above is not clear or you wish to discuss any of the points please do not hesitate to call myself or any of the other committee members.

We wish you well in completing your study and are looking forward to hearing about your findings.

If you make any major change in your project please notify the Committee.

Sincerely,

Margaret Louis

Margaret Louis, RN PhD
Chairperson
Human Subjects Rights Committee
Department of Nursing, UNLV

CC:M. Louis, Ph.D.

APPENDIX D

DATA COLLECTION FORM

ID #_____

Date_____

Pap result_____(normal/abnormal)

Naked eye observation, aceto-white_____(yes/no)

Colposcopy observation, aceto-white_____(yes/no)

APPENDIX E

CORRESPONDENCE

Premier Medical Center 12/3/96
111 East Harmon
Las Vegas, Nevada 89101

Dear Doctor Friedman,

I am a graduate student at UNLV, in the Nurse Practitioner Program. Terry McKnight APN, is my preceptor at Premier Medical Center. My program requires a Masters thesis. I have chosen to look at an aspect of womens health. Specifically what I am looking for is validation of the naked eye observation of the cervix after application of acetic acid. In order to do this I will screen for cervical dysplasia/cancer in three ways. The first is the Pap, the second is viewing the cervix with my naked eye after application of an acetic acid solution, and the third is viewing the cervix through the colposcope after application of an acetic acid solution.

In order to complete this study I need your help. First, I am asking to use your clinic and its population as my setting and sample. I will need to do approximately 150 Paps. Secondly, I need your permission to use your colposcope. After receiving written permission from each subject, I plan to do the routine Pap, next I will apply acetic acid to the cervix, observe it, and record either a normal or abnormal result. Finally I will view the cervix through the colposcope and record either a normal or abnormal result. All procedures will be done under the direct supervision of Terry McKnight RN, APN. What this means is that all Paps in the study would also be screened with the naked eye and the colposcope. Under no circumstance would a biopsy be taken.

My program has already included training in the Pap procedure. It does not include training in colposcopy. For this I have been observing colposcopys at Nellis Federal Hospital under the supervision of Major B.J. Reyes,RN,APN. I have spent approximately 40 hours with her learning to interpret the normal and abnormal cervix. Before any testing is done the thesis proposal will get approval from the UNLV Human Subjects Rights Committee.

Currently there is a contract between UNLV and Premier Medical Center. This has allowed me to use your site as a clinical area, for which I am grateful. I also carry my own liability insurance, and there is a copy on file at the Clinic. Having talked with my Nursing Department I assure you that both of these things protect Premier Medical Center from any potential liability.

If you have any questions that I could answer, that would help you in your decision to say yes, please don't hesitate to call me. I would be happy to meet with you and explain the thesis in more detail. I will try to publish the results and if I do of course I will acknowledge Premier Medical Center if you choose this. Thank you for your time, and I anxiously await your answer.

Yours truly,

Carol Schmidt RN, FNP student

Carol Schmidt RN, FNP student 454-9583
1403 Bareback Court.
Henderson, NV 89014

12/3/96
OB/GYN Department
Nellis Federal Hospital
Las Vegas, Nevada

Dear Sir,
I am a graduate student at UNLV, in the Nurse Practitioner Program. My program requires a Masters thesis. I have chosen to look at an aspect of womens health. Specifically I am looking for is validation of the naked eye observation of the cervix after application of acetic acid. In order to do this I will screen for cervical dysplasia/cancer in three ways. The first is the Pap, the second is viewing the cervix with my naked eye after application of an acetic acid solution, and the third is viewing the cervix through the colposcope after application of an acetic acid solution.

In order to complete my study I need your help. First, I am asking to use your clinic and its population as my setting and sample. I will need to do approximately 150 Paps tests. Secondly, I need your permission to use your colposcope. After receiving written permission from each subject, I plan to do the routine Pap. Next I will apply acetic acid to the cervix, observe it, and record either a normal or abnormal result. Finally I will view the cervix through the colposcope and record either a normal or abnormal result. What this means is that all Paps in the study would also be screened with the naked eye and the colposcope. These procedures will be done under the direct supervision of Major Reyes. Under no circumstances would any biopsy be taken. Before any testing is done the thesis proposal will get approval from the UNLV Human Subjects Rights Committee.

My program has already included training in the Pap procedure. It does not include training in colposcopy. For this I have been observing colposcopys at Nellis Federal Hospital under the supervision of Major B.J. Reyes,RN,APN, director of the dysplasia clinic at Nellis Federal Hospital. She has graciously volunteered her time and instructed me in normal and abnormal interpretation of the cervix, both with the naked eye and through the colposcope. I have spent approximately 40 hours with her.

If you have any questions that I could answer that would help you in your decision to say yes, please do not hesitate to call me. I would be happy to meet with you and explain the thesis in more detail. I will try to publish the results when I finish and if I do, of course, I will acknowledge your facility and the help I have received from Major Reyes. Thank you for your time, and I anxiously await your answer.
Yours truly,

Carol Schmidt RN, FNP student 454-9583
1403 Bareback Ct.
Henderson, NV 89014

Arlene Carter RN APN 1/15/97
Clark County Health District
625 Shadow Lane
Las Vegas, Nevada 89127

Dear Arlene,

I am a graduate student at UNLV, in the Family Nurse Practitioner Program. I have completed my clinical time and am trying to finish my Masters thesis. I have chosen to look at an aspect of womens health. Specifically what I am looking for is validation of the naked eye observation of the cervix after application of acetic acid, and the use of this observation as a way to augment the Papanicolaou screening test. In order to do this I need to screen for cervical dysplasia/cancer in three ways. The first is the Pap, the second is viewing the cervix with my naked eye after application of an acetic acid solution, and the third is viewing the cervix through the colposcope after application of an acetic acid solution.

In order to complete my study I need your help. I am asking to use your clinic and its population as my setting and sample. I will need to do a total of approximately 150 observations. Not all of these need to come from your clinic.

My plan to accomplish these observations is simply by being in the room when the Pap procedure is being done, and observing the cervix and recording the observation. After the acetic acid is applied to the cervix by the provider and the provider has viewed the cervix, I will look at the cervix too, and record the result. Next I will look at the cervix through the colposcope and record the observation. Of course this would be done after receiving written permission from each subject.

This thesis proposal has received approval from the UNLV Human Subjects Rights Committee. Currently I have permission and am collecting data from two other sites, Nellis Federal Hospital and Premier Medical Center.

My program has included training in the Pap procedure. It does not include training in colposcopy. For this I have been observing colposcopys at Nellis Federal Hospital under the supervision of Major B.J. Reyes, RN, APN, director of the dysplasia clinic at Nellis Federal Hospital. She has instructed me in normal and abnormal interpretation of the cervix, both with the naked eye and through the colposcope. I have spent approximately 40 hours with colposcopy interpretation. If you have any questions that I could answer that would help you in your decision to say yes, please do not hesitate to call me. I would be happy to meet with you and explain the thesis in more detail. Thank you for your time, and I anxiously await your answer.
Yours truly,

Carol M Schmidt RN FNP student

Carol Schmidt RN, FNP student 454-9583
1403 Bareback Ct.
Henderson, NV 89014

Carol Schmidt RN, FNP student 454-9583
1403 Bareback Ct.
Henderson, NV 89014

Dear Carol,
I, Lane Friedman MD, Medical Director at Premier Medical Center, in Las Vegas Nevada, will allow Carol Schmidt RN, FNP student, permission to conduct her research at the Premier Medical Facility. She has permission to use the colposcope at the facility and has been granted access to the population. I understand the Premier will assume no legal liability associated with this research, and there will be no cost to the facility. I understand that no research will be done until it has the approval of the University of Nevada, Las Vegas Human Right Review Committee. The clinic will remain anonymous unless I decide otherwise.
Yours truly,

Lane Friedman MD,

Medical Director
Premier Medical Center
111 East Harmon
Las Vegas, Nevada 89101

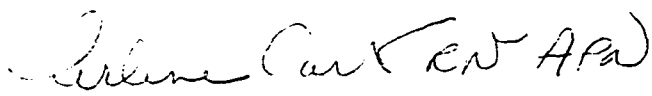
Carol Schmidt RN, FNP student 454-9583
1403 Bareback Ct.
Henderson, NV 89014

Dear Carol,
I, Major B.J. Reyes RN APN, Director of the Dysplasia Clinic, give Carol Schmidt RN, FNP student, permission to conduct her research in the OB/GYN clinic at Nellis Federal Hospital. She has permission to use the colposcope at the facility and has been granted access to the population. I understand there will be no cost to the facility for this research. I understand that no research will be done until it has the approval of the University of Nevada, Las Vegas Human Right Review Committee. The clinic will remain anonymous unless I decide otherwise.
Yours truly,

Major B.J.Reyes RN APN
Director of the Dysplasia Clinic
OB/GYN Department
Nellis Federal Hospital
Las Vegas, Nevada

Carol Schmidt RN, FNP student 454-9583
1403 Bareback Ct.
Henderson, NV 89014

Dear Carol,
I, Arlene Carter RN APN, Clinic Supervisor of the Clark County Health District, in Las Vegas Nevada, will allow Carol Schmidt RN, FNP student, permission to conduct her research at the Clark County Health Districts Clinic. She has permission to make observations of the cervix with the use of the colposcope at the facility and has been granted access to the population. I understand the Clinic will assume no legal liability associated with this research, and there will be no cost to the facility. The clinic will remain anonymous unless I decide otherwise.
Yours truly,



Arlene Carter RN APN,

Clinic Supervisor
Clark County Health District
625 Shadow Lane
Las Vegas, Nevada 89127

APPENDIX F

COLPOSCOPY OBSERVATION CERTIFICATION

Carol Schmidt RN, FNP student 454-9583
1403 Bareback Ct.
Henderson, NV 89014

Dear Carol,
This is to certify that you have had 40 hours of colpolscopy training in the dysplasia clinic at Nellis AFB, under the direct supervision of myself, Major B.J. Reyes, RN. APN., Director of the Dysplasia Clinic at Nellis AFB. This training has included observation of the transformation zone of the cervix, with and without the colposcope, and identification of normal and abnormal cervices after application of acetic acid, with and without the colposcope. If there is any way that I can assist you in your study, do not hesitate to call me.
Yours truly,

Major B.J. Reyes, RN, APN

Director of the Dysplasia Clinic
OB/GYN Department
Nellis Federal Hospital
Las Vegas, Nevada

ASSOCIATED PATHOLOGISTS LABORATORIES

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4230 Burnham Avenue
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W. Howard Hoffman, M.D
Jean E. McCusker, M.D
Carol A. van der Harree-Alger, M.D
Sue Gunasegaram, M.D
Craig A. Voss, M.D
David A. Miller, M.D
Peter A. Scully, M.D
Elizabeth D. Iole, M.D.
Bob Daniel, M.D.
Mitchell S. Wachtel, M.D.
Jeffrey S.H. Tsang, M.D.

Scientific Staff:
Beata M. Cornett, Ph.D
John E. Hunt, Ph.D.
Charles F. Piese, Ph.D.
Raymond C. Kelly, Ph.D. DABFT

APPENDIX G

APL LICENSURE

ASSOCIATED PATHOLOGISTS LABORATORIES
LABORATORY CERTIFICATION AND ACCREDITATION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
- -CLIA 88 Registration Certificate #29D0652720
- -Medicare Provider #29-8013

NATIONAL INSTITUTE OF DRUG ABUSE (NIDA)

NEVADA STATE LICENSED LABORATORY
- -License #4
- -Medicaid Provider #42-02239

COLLEGE OF AMERICAN PATHOLOGISTS
- -Lab #22466-01
- -Last Inspection 2/96

AMERICAN ASSOCIATION OF BLOOD BANKS

1966 30 YEARS OF EXCELLENCE 1996

APPENDIX H

COPYRIGHT/QUOTATIONS PERMISSION FORM

October 7, 1996

W.B. Saunders Company
The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Attention Julie Lawley

Dear Ms. Lawley,

I am a graduate student in nursing at the University of Nevada Las Vegas. W. B. Saunders has published a book which has a diagram that I would like to use in my thesis. The name of the book is Essentials of Obstetrics and Gynecology. It was published in Hacker & Moore 1992 and is the second edition. The diagram is on page 589 and is labeled Figure 54-1. It is a great diagram and I want to use it to clarify cervical landmarks for the reader. I appreciate your help in this matter.

Yours truly,

Carol M Schmidt

Carol Schmidt
1403 Bareback Ct.
Henderson, Nevada 89014

702-454-9583

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Julie Lawley 11/3/96
W. B. Saunders Company Date

One time use only