SUMMARY

Phenethicillin, ampicillin and tetracycline were given by a randomized method to 97 children suffering from 112 separate episodes of pneumonia. The dose of each antibiotic given was 40 mg./kg./day by mouth in divided doses at eight-hour intervals.

Assessment of the effects of the three antibiotics was measured by the rate at which the temperature returned to normal, the WBC after 10 days' treatment and the rate at which the chest film cleared. It was found that there were no particular advantages to any one of the antibiotics as measured by the above methods. It was also found that in this entire group of patients the rate of clearing was rapid no matter what the etiology of the individual case.

The authors wish to express their appreciation to Dr. Leighton Smith of Ayerst McKenna & Harrison Limited for supplies of phenethicillin (Brocsil) and ampicillin (Penbritin).

REFERENCES

1. KLEIN, J. O. AND FINLAND, M.: *New Eng. J. Med.*, **269**: 1019, 1963.
2. TRAFFORD, J. A. P. *et al.*: *Lancet*, **1**: 897, 1962.
3. Subcommittee of the Antibiotics Clinical Trials (Non-tuberculous) Committee of the Medical Research Council: *Brit. Med. J.*, **2**: 1361, 1951.
4. KIRBY, W. M. M. *et al.*: *J. A. M. A.*, **147**: 110, 1951.
5. AUSTRIAN, R. *et al.*: *Bull. Hopkins Hosp.*, **91**: 323, 1952.
6. AUSTRIAN, R. *et al.*: *Ibid.*, **89**: 407, 1951.
7. WALLMAN, I. S. AND HILTON, H. B.: *Lancet*, **1**: 827, 1962.

The Irrigation Smear—A New Cytodiagnostic Technique for the Detection of Cancer of the Uterine Cervix

GEORGE H. ANDERSON, M.B., B.S. and KURT KRAKAUER, R.T.[C],
Ottawa, Ont.

Using the Davis cytopipette, cytologic smears were prepared from 2014 patients; 1367 of these specimens were obtained by the patients themselves. The series included 57 cases of carcinoma or atypia of the cervix, and 50 (88%) of these cases were found to have abnormal cells in the irrigation smear.

Cytopipette samples were obtained by a nurse from 647 Eskimos, but cell preservation in this group was not satisfactory because of a delay of several weeks in preparing the smears. Accurate results depend also on specific training of the personnel reading the smears because fewer cells may be present in these smears than in cervical scrape smears.

The irrigation smear is recommended as a reasonably accurate method of screening women for cancer of the cervix if they are not being examined regularly by the cervical scrape method. Hospital admissions of females may be a fruitful source of such cases.

Utilisant une cytopipette de Davis, on a préparé des frottis cytologiques provenant de 2014 patientes; 1367 de ces échantillons avaient été prélevés par les femmes elles-mêmes. On a découvert 57 cas de cancer ou de tumeur atypique du col et, dans 50 de ces cas (88%) on avait découvert des cellules anormales dans le frottis post-irrigation.

Une infirmière a ainsi prélevé par cytopipette des échantillons chez 647 Esquimaux, mais la conservation cellulaire n'a pas été jugée satisfaisante en raison d'un retard de plusieurs semaines pour la préparation des frottis. La précision des résultats est aussi fonction de la formation speciale reçue par le personnel qui lit les frottis, ceux qui sont préparés par la nouvelle méthode contenant moins de cellules anormales que les frottis par prélèvement direct sur le col.

Le frottis post-irrigation est à conseiller comme méthode raisonnablement précise pour le dépistage du cancer cervical, surtout chez les femmes qui ne sont pas examinées régulièrement par la méthode classique des frottis obtenus par raclage. Les femmes qui sont admises dans les hôpitaux peuvent constituer des candidates tout indiquées pour cette méthode.

DESPITE the proved reliability of the cytologic method for the early detection of cancer of the uterine cervix, the majority of the female population of North America as yet do not avail themselves of this test.

The reasons for this have included unwillingness of physicians to perform the test; lack of skilled technicians and pathologists to examine the smears; and the unwillingness of asymptomatic women to subject themselves to a pelvic examination. The latter is probably the most important reason why so many women are still not screened on this continent.

In an attempt to solve this problem, Dr. Hugh Davis of the Johns Hopkins Hospital developed an easily performed douche method

From the Cytology Laboratory, Department of Pathology, Ottawa Civic Hospital, Ottawa, Ontario.
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Reprint requests to: Dr. George H. Anderson, Department of Pathology, Ottawa Civic Hospital, Carling Avenue, Ottawa, 3, Ontario.

of sampling the cell content of the upper vagina and ectocervix;[1, 2] this technique can be used at home by the patient herself, or by a nurse in a clinic. A plastic disposable pipette containing an irrigating solution is used to lavage the cervix and upper vagina. The resultant cell suspension is drawn back into the pipette, which can then be mailed to the laboratory for processing.

In the summer of 1964 at the Ottawa Civic Hospital we started to investigate the reliability of this method, using the Davis cytopipette in the following groups of people: (1) public patients attending the outpatient department and in hospital, and the private patients of staff obstetricians and gynecologists; (2) Eskimos surveyed from a government ship (the *C. D. Howe*), during its annual trip to the Eastern Arctic during the summer of 1965.

Cytopipettes have been used by 2014 patients in this series and the results obtained with this group of patients are presented in this report. As many patients as possible also had vaginal and cervical smears prepared by conventional methods to provide a control of the accuracy of the cytopipette.

METHOD OF OBTAINING AND PROCESSING SMEARS

Each patient in the first group was given a cytopipette and an instruction sheet similar to that described by Davis.[1, 2] The public patients were asked to use the pipette immediately and return it to the clinic nurse. Private patients were provided with a mailing container and were asked to use the pipette during mid-cycle at home and return it to the laboratory by mail. All the patients in the Eskimo group had their samples obtained by a nurse on the ship.

The processing of the cytopipettes and smears was carried out as recommended by Davis.[1, 2] The technologist (K.K.) assigned to this project spent two weeks in Davis' laboratory to acquire first-hand knowledge of the processing and cytodiagnostic methods used there. In brief, smears are prepared from the centrifuged deposit of cells in the cytopipette, and are then stained using a modification of the Papanicolaou method.

RESULTS

These will be presented in two groups: (1) the patients who used the cytopipette themselves and (2) the Eskimo patients.

Group 1

Of 1367 patients who used the cytopipette themselves 709 or 52% had corroborative Papanicolaou smears obtained by conventional methods.

When comparing the cellular content of the 709 routine cervical scrape smears with the irrigation smears from these same patients in Group 1, few significant differences were observed in the type of smear obtained. This is contrary to the finding of Macgregor, Fraser and Mann,[4] who stated that inflammatory cells, red blood cells, trichomonads and monilia "are infrequently seen in an irrigation smear". In our experience where these non-epithelial elements were seen in the cervical scrape smears they were also seen in the majority of the irrigation smears of the same patients.

This group of 1367 patients includes 57 patients with carcinoma or atypical hyperplasia of the cervix, seven patients with adenocarcinoma of the endometrium and one patient with metastatic adenocarcinoma of the thyroid—65 patients. The results obtained with this group of 65 patients, selected for this series to test the accuracy of the method, are presented in Tables I and II. Because the author (K.K.) who screened all the slides in this series also works in our routine cytology laboratory, he was aware of which cases had been selected in the majority of instances.

TABLE I.—CORRELATION OF CERVICAL SCRAPE CYTOLOGY WITH IRRIGATION SMEAR CYTOLOGY: GROUP I

Biopsy diagnosis	*Detected in cervical scrape*	*Detected in irrigation smear*	*Accuracy in interpretation irrigation smear %*
Cancer of cervix, invasive.....	26	24	92
Cancer of cervix, preinvasive.....	24	20	83
Atypia cervix...	7	6	86
Total....	57	50	88

TABLE II.—ENDOMETRIAL AND METASTATIC TUMOURS DETECTED IN THE IRRIGATION SMEAR: GROUP I

Biopsy diagnosis	*Detected in irrigation smear*	*Accuracy of interpretation of irrigation smear*
Adenocarcinoma of endometrium, seven cases.....	5	71%
Adenocarcinoma of thyroid, metastatic, one case.....	1	

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Fifty of the 57 cases of carcinoma or atypia of the cervix produced smears in which atypical or malignant cells were reported—an accuracy of 88%. Five of the seven cases of endometrial adenocarcinoma produced reports of positive smears, an accuracy of 71%.

Of the seven cases of carcinoma or atypia of the cervix missed by the cytologist examining irrigation smears, three were missed because the specimens were inadequate, containing too few cells for interpretation; of two cases of endometrial adenocarcinoma missed in the irrigation smears one was missed because the specimen was inadequate. On careful rescreening of the remaining five cases missed in examination of the irrigation smears, no atypical cells were found in any of the smears.

In a survey of an unscreened population all the patients with inadequate specimens would be sent another cytopipette, and if this still did not produce a readable smear, the patients would be advised to attend their doctor's office for a routine cervical scrape smear.

TABLE III.—A COMPARISON OF INADEQUATE IRRIGATION SMEARS FROM OFFICE AND CLINIC PATIENTS: GROUP I

Office patients	904	36 (4%) inadequate
Clinic patients	463	50 (11%) inadequate
Total	1367	86 (6%) inadequate

An analysis of the inadequate smears produced by the 1367 patients who used the cytopipettes themselves is presented in Tables III and IV.

TABLE IV.—A COMPARISON OF INADEQUATE IRRIGATION SMEARS FROM PRE- AND POST-MENOPAUSAL PATIENTS: GROUP I

Premenopausal patients	963	39 (4%) inadequate
Postmenopausal patients	404	47 (12%) inadequate

The marked difference in the results obtained from the clinic patients and the office patients is interesting and may be partly accounted for by the fact that the clinic patients were asked to obtain their specimens at the time of their visit to the clinic. These specimens were thus obtained in strange surroundings, perhaps less conducive to good results than in the case of the office patients who obtained their specimens at home. The office patients were asked to use the cytopipette during mid-cycle, which tends to result in a better specimen than at other times of the cycle. Finally, the incidence of Trichomonas infestation and other inflammatory diseases is usually higher in clinic than in office patients, thus modifying the quality of the smears obtained from the clinic patients. Despite these differences, there seems to be little doubt that the lower the socioeconomic status of the patients using the cytopipette the higher the percentage of inadequate specimens obtained.

The difference in the results obtained by the pre- and post-menopausal groups is what one might expect and reflects the normal difference in exfoliation between these two age groups.

Group 2

Table V presents the results from the survey of 647 Eastern Arctic Eskimos.

TABLE V.—CYTOPIPETTE SURVEY OF 647 EASTERN ARCTIC ESKIMOS: Group II

Satisfactory smears	294 cases	45%
Smears not diagnostic—loss of cell detail	321 cases	50%
Smears not diagnostic—too few cells	32 cases	5%
Smears with Trichomonas infestation	150 cases	23%
Positive or suspicious smears	None	
Average age	31 years	

Approximately one-half of these specimens were inadequate for interpretation because of loss of cell detail, particularly nuclear detail. This disappointing result is attributed to the fact that the cytopipettes were not processed until the end of the survey, which extended over a two-month period in midsummer, and they were stored at room temperature after collection. In a number of the pipettes bacterial growth had occurred and positive cultures were obtained from these pipettes. This problem can be overcome in one of two ways: either the cytopipettes may be processed within a few days of collection or they may be frozen and stored indefinitely. In a preliminary study of the irrigation smear Anderson and Krakauer[3] reported that cell detail is well preserved in frozen specimens, and that this technique would be used in a further Eskimo survey being undertaken during the summer of 1966.

The Eskimo, who 10 years ago had a life expectancy at birth of only 35 years, can now expect to live until 45 or 50. This life expectancy will almost certainly continue to increase. Carcinoma of the cervix may be expected to become a significant cause of death as the older Eskimo population increases, particularly in view of the early age at which sexual intercourse starts and the generally poor genital hygiene among the Eskimos. Because of the limited space available on the survey ship, the cytopipette may prove to be an ideal method of screening this population when the problem of the long-term preservation of cell detail in the cytopipette has been overcome.

Among the Eskimo group the low incidence of smears (5%) which were not diagnostic because there were too few cells in the smear shows that, when used by a trained nurse or technician, the cytopipette is capable of very adequate sampling of the cell population of the ectocervix and upper vagina. In a small group of Indians on the Manitoulin Island Reserve from whom cytopipette samples were obtained, a similar high proportion of adequate samples was seen. No smears with atypical or malignant cells were found in the Eskimo group, but in view of the high proportion (55%) of inadequate smears, this finding has little significance.

DISCUSSION

Over the past four years a number of papers have appeared in the literature concerning the cytopipette. Some attributed a relatively high degree of accuracy to it;[1-3, 7, 8] others suggested that the cytopipette is an extremely inaccurate means of screening a population for cancer of the cervix;[4, 9, 13] while a third group of investigators found the reliability of the method to fall between these two extremes.[6, 10]

The present authors now subscribe to this last view. We believe that a method which in our hands is of the order of 10% less accurate than the cervical scrape technique should not be recommended as the method of choice. Indeed, Davis in his original article emphasized that the cytopipette was not intended to replace a complete physical examination and cervical scrape smear in the doctor's office. Nevertheless we believe that the cytopipette has a most important role to play in detecting early, asymptomatic cervical cancer months or years before it would otherwise have been detected, in women who do not present themselves regularly to a physician for a complete physical examination.

It is preferable to detect 88% of cancers of the cervix at an early, asymptomatic and often preinvasive stage, using a less than ideal method from the point of view of accuracy, than to wait until these same women develop symptomatic invasive cancers.

The thousands of women admitted to hospital each year for non-gynecological complaints are an important potential source of such cases. The majority of women do not have a cervical scrape smear as part of their routine investigation and have never had one previously. Both Liu[11] and Handy and Wieben,[12] in articles on the routine screening of female hospital admissions for cancer of the cervix, reported a case-finding rate of 4 per thousand, indicating that the female hospital population is indeed a fruitful area of investigation. In the Ottawa Civic Hospital, with approximately 10,000 female admissions per year, excluding pediatric admissions and admissions to the maternity unit, we expect to pick up about 40 unsuspected cases of non-invasive cancer of the cervix per year when our in-patient cytodiagnostic program, using the cytopipette, goes into effect.

As with more conventional cytology methods, a bonus from this technique is the detection of a number of unsuspected cases of adenocarcinoma of the endometrium. In our seven cases of endometrial adenocarcinoma, the cytopipette had an accuracy of 71%, similar to that found with conventional vaginal pool smears.

A most important observation, first pointed out by Bredahl, Koch and Stakemann,[5] is that experience in the interpretation of irrigation smears is essential before the method can be considered reliable. Even well-trained cytotechnologists inexperienced in the interpretation of irrigation smears will miss as many as 30% of positive smears. This is because the irrigation smear tends to present the screener with single cells rather than groups of cells, so that the cytotechnologist must be re-educated to respond to this lesser evidence. However, this does not represent a serious problem, since the technologist responsible for screening this series of irrigation smears (K.K.) became proficient at screening them during a two-week visit to Davis' laboratory.

Once the technologist learns to recognize abnormal cells in the irrigation smear, screening becomes relatively easy. The cells are evenly dispersed in a uniform monolayer and can be rapidly scanned by an experienced technologist. Since additional material usually remains in the pipette, extra slides can be prepared to help confirm any abnormal finding. Many "teaching" slides can be prepared from one pipette.

Apart from its cancer-screening potential, the cytopipette can be of value to the clinician in the patient who requires frequent hormonal estimations. Instead of having to visit the doctor's office on numerous occasions to have a smear made, the patient is given a supply of cytopipettes to take home and instructed to use them on specified dates, and then to mail them to the laboratory.

Anderson and Clark[6] recently reported that the cytopipette may also be used to obtain specimens from patients in whom it is not possible to pass a speculum because of contracture produced by previous radiotherapy or operation.

SUMMARY

Irrigation smears from 2014 patients were prepared after using the Davis cytopipette. Of these, 1367 specimens were obtained by the patients themselves, and this group included 50 cases of carcinoma of the cervix and seven cases of atypical hyperplasia of the cervix. Fifty of these 57 cases with lesions of the cervix were found to have abnormal cells in the irrigation smear, for an accuracy of 88%. Five of seven cases of adenocarcinoma of the endometrium also had abnormal cells in the irrigation smear, an accuracy of 71%.

A group of 647 Eskimos had cytopipette samples obtained by a nurse. These were not processed until several weeks after collection and showed loss of cell detail in a high proportion of cases. It appears that the cytopipette sample must be processed within a few days of collection or frozen for adequate preservation of cell detail. A prerequisite to obtaining accurate results with this technique is that the personnel examining these smears must first have specific training in reading irrigation smears.

It is concluded that the irrigation smear technique is a reasonably accurate method of detecting cancer of the cervix in asymptomatic women. Its use is recommended for those segments of the population who at the present time are not being examined regularly by the cervical scrape method. In particular it is suggested that female hospital admissions may be a fruitful source of cases, since the majority of these patients have not had a cytologic examination previously.

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REFERENCES

1. DAVIS, H. J.: *Acta Cytol. (Balt.)*, **6**: 459, 1962.
2. *Idem*: *Amer. J. Obstet. Gynec.*, **84**: 1017, 1962.
3. ANDERSON, G. H. AND KRAKAUER, K.: *Acta Cytol. (Balt.)*, In press.
4. MACGREGOR, J. E., FRASER, M. E. AND MANN, E. M. F.: *Lancet*, **1**: 252, 1966.
5. BREDAHL, E., KOCH, F. AND STAKEMANN, G.: *Acta Cytol (Balt.)*, **9**: 189, 1965.
6. ANDERSON, A. F. AND CLARK, F. R.: *Lancet*, **1**: 479, 1966.
7. DAVIS, H. J. AND KURZ, L.: *Danish Med. Bull.*, **9**: 121, 1962.
8. KOCH, F. AND STAKEMANN, G.: *Ibid.*, **9**: 127, 1962.
9. RICHART, R. M. AND VAILLANT, H. W.: *J. A. M. A.*, **192**: 199, 1965.
10. ANDERSON, W. A. D. AND GUNN, S. A.: *CA(N.Y.)*, **15**: 158, 1965.
11. LIU, W.: *Obstet. Gynec.*, **26**: 518, 1965.
12. HANDY, V. H. AND WIEBEN, E.: *Obstet. Gynec.*, **25**: 348, 1965.
13. MUSKETT, J. M., CARTER, A. K. AND DODGE, O. G.: *Brit. Med. J.*, **2**: 341, 1966.

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