

A preliminary summary of the results of cytological examinations on 600,000 women indicates the efficacy of widespread use of cytology to detect cancer of various organs.

Uterine Cytology

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THE USE of exfoliative cytology to detect cancer of the uterus is now accepted in many areas of this country. Eight years ago, only a few thousand women were receiving an annual uterine cytology examination. Now it is estimated that each year more than 3 million women receive cervical cancer examinations using the cytological method.

The recognition of exfoliative cytology as a practical means of detecting early cancer of the uterine cervix was preceded by years of research. Among those groups responsible for the widespread acceptance and employment of the technique is the National Cancer Institute, whose investigators have pioneered in the application of cytology to detection of human cancer in large population groups.

The institute was one of the first agencies to recognize the potentialities of the cytological work of Papanicolaou, Traut, and others whose reports had been largely overlooked by pathologists and clinicians until after World War II. At that time, institute investigators

were evaluating a number of cancer "tests" described in the literature, and the cytological method was one of the few that appeared to merit further investigation.

In 1947, scientists of the National Cancer Institute established a study at Hot Springs, Ark., to evaluate the cytological technique as an aid to diagnosis of cancer of the uterine cervix. In the process of testing the method on women admitted to the venereal disease center, the investigators satisfactorily resolved many problems relating to the administration of such projects and provided some direction to basic problems of human cancer which may be studied using exfoliative cytology. On the basis of this experience, 4 years later the institute moved the project to Memphis, Tenn., to determine the practicality of vaginal cytology as a general population study procedure and to gather epidemiological information.

Preliminary data encouraged the establishment and operation of several other uterine cytology projects in order to develop new methods and techniques, investigate pathogenesis, and improve epidemiology procedures. These were set up at Columbus, Ohio; Louisville, Ky.; Madison, Wis.; New York, N.Y.; Philadelphia, Pa.; San Diego, Calif.; Washington, D.C.; Providence, R.I.; Detroit, Mich.; and Charlotte, N.C. Some of the projects have been directly administered by the institute, while others have been operated through grants to universities and medical schools. In each

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situation there has been a high degree of cooperation with local health and medical groups and with individual physicians and pathologists.

The goal of the program is the cytological examination and evaluation of no fewer than 700,000 women tested once, 210,000 tested a second time, and 70,000 tested three times. It would be preferable, of course, to reexamine a larger percentage, but experience to date indicates that 30 percent is the best yield that can be expected on return examinations. At present, more than 600,000 women have been examined at least once.

A Single Research Experience

Although the women studied represent a number of widely separated population groups, certain uniform procedures and standards make it possible to view the entire group as a single research experience.

In all cases, the fixation and staining of the slide material have been accomplished by using the Papanicolaou technique. Examination of the smears for malignant cells or for evidence of abnormal cellular changes has followed the procedure originally established at Memphis. This system, referred to as a "pyramid," features step-by-step screening of smears by increasingly competent and experienced technicians, and final interpretation of suspicious smears by a pathologist.

All the projects have employed a standard code system of reporting data to a single evaluation center. The coded information includes patient identification, cytological examination and biopsy results, clinical or surgical findings, and data necessary for proper clinical evaluation and epidemiological study. In order to assay epidemiological factors in cancer of the uterine cervix, a record has been made of each patient's age, race, geographic location, marital status and pregnancy history, socioeconomic status, and ethnic or religious status.

There are, of course, some variations in procedure. The techniques for obtaining material for cytological examination include vaginal aspiration, cervical scraping, and cotton swab wiping, accomplished by using glass or plastic pipettes, plastic "straws," or wooden spatulas

or applicators. The specimens were collected by physicians, nurses, or medical or nurses' aides.

Some of the Findings

Thus far, 608,200 women have been examined the first time. Their laboratory smear reports are indicated in table 1. The designation "unsatisfactory" may refer to insufficient material on the smear, inadequate staining, loss of material, or breakage of the slide before interpretation. "Negative" smears are considered totally negative for cancer, and "atypical" indicates those smears that are negative for cancer but indicate some sort of epithelial cell abnormality. "Suspicious" means the smear shows some cells which may indicate the presence of cancer. Finally, "positive" indicates definite evidence of cancer.

By using raw, unpublished data, it has been possible to compute gross rates for various kinds of cancer found in the first examination of the entire group (table 2). Consideration of the number of intraepithelial cancers of the cervix compared with the number of invasive cancers of the cervix may shed some light on the relationship of intraepithelial carcinoma to

Table 1. Results of first cytology examination of 608,200 women

Result	Number examined	Percent
Unsatisfactory.....	5, 660	0. 9
Negative.....	578, 640	95. 2
Atypical.....	18, 430	3. 0
Suspicious.....	4, 010	. 7
Positive.....	1, 460	. 2
Total.....	608, 200	100. 0

Table 2. Proved cancers detected as a result of first cytological examination of 608,200 women

Type of uterine cancer	Number patients	Rate per 1,000
Intraepithelial carcinoma of cervix..	1, 490	2. 45
Invasive carcinoma of cervix.....	910	1. 50
Cancer of corpus.....	130	. 21
Cancer of other sites of female reproductive tract.....	55	. 09

invasive carcinoma. Certain fundamental questions concerning this relationship have been summarized previously (1):

- Do all invasive cervical cancers begin as intraepithelial lesions?
- What proportion of intraepithelial lesions progress to invasive lesions?
- What is the time required for an intraepithelial lesion to progress to invasiveness?
- Do some intraepithelial lesions regress and disappear spontaneously?
- Is it possible for an intraepithelial lesion to remain noninvasive indefinitely?
- What are the age-specific incidence and prevalence rates of carcinoma-in-situ and invasive carcinoma?

Table 3, which is compiled from published material, shows considerable variation between studies in the proportion of intraepithelial and invasive cervical carcinomas found at first examination. Further analysis may reveal that this variation is due to different epidemiological factors in the separate study groups.

The women screened in the Madison study (2) were predominantly rural residents examined by their private physicians. The group was comprised of women 20 years of age or over, and included only a few Jewish or Negro women. The investigators suggested that the particularly high prevalence rates for invasive cervical cancer in Madison indicated that the physicians taking the smears were selecting women with suspected lesions. They reported, however, that the more recent trend has been to examine larger numbers of asymptomatic women, with a concomitant decrease in the percentage of total malignant tumors detected and a relative increase in the number of intraepithelial carcinomas discovered.

The study group in Hot Springs (3) included females in the cancer-age group who were admitted to the venereal disease center. The minimum age was sometimes 35, sometimes 40, in this study, and the study group was 93 percent Negro.

Dunn and his associates (4) reported that over two-thirds of their study group were patients of gynecologists and obstetricians, and the remainder were examined by other private physicians in metropolitan San Diego. The minimum age was 15 years, and relatively few

Table 3. Uterine cancers diagnosed microscopically following first cytological examination

Project	Number screened	Cancer of the cervix	
		Intraepithelial	Invasive
Memphis.....	108, 136	393	373
Madison.....	65, 163	206	335
Columbus.....	37, 540	31	52
San Diego.....	33, 746	259	77
Louisville ¹	12, 000	41	60
Hot Springs.....	3, 224	32	35

¹ SOURCE: W. M. Christopherson and J. E. Parker: Cervical cell studies. A method of increasing production. J.A.M.A. 108: 1718-1719 (1958).

women over 50 were examined. The women were white and gentile.

In Columbus (5), 73 percent of the study group were examined by private physicians; the remainder were examined in various clinics. In their preliminary report, Ullery and his co-workers did not discuss age or race, except to state that the minimum age was 20 years.

Erickson and others (6) reported that their study patients, all 20 years of age or older, were examined in health department and hospital clinics, or in temporary clinics set up in industrial and business concerns, or by physicians in private practice. Approximately 13 percent of the women examined were not residents of Shelby County, the designated test area, but were women who came to Memphis physicians for medical care and were therefore a selected group such as will be found in any hospital sampling. Of the 373 women with invasive uterine cancer, 36 percent were nonresidents. However, the rate of occurrence of intraepithelial carcinoma was similar for residents and nonresidents, as would be expected for an asymptomatic, unsuspected lesion. The authors also found that whereas one-third of the surveyed population were Negroes, two-fifths of all the intraepithelial carcinomas found were among Negroes.

Rate Comparisons

The Memphis study produced a casefinding rate 40 times that observed in the community

prior to the establishment of the project. Among the 108,136 women examined the first time, 60.4 percent, or 463 of the 766 cases of invasive uterine and intraepithelial cervical carcinoma found, were unsuspected. Of the 393 cases of intraepithelial carcinoma, 90 percent were unsuspected; 30 percent, or 112, of the 373 cases of invasive carcinoma were unsuspected. In addition, 20 cases of extrauterine genital cancer were found. These cases are not included in this analysis.

In Columbus, of the 99 patients found to have cancer of the genitalia—intraepithelial and invasive cancers of the cervix, and cancers of the corpus uteri, vagina, and ovary—69 percent had cancers that were previously unsuspected.

The Madison investigators reported that 74 percent of the confirmed cases of intraepithelial cancer of the cervix were not clinically detectable. The opposite relationship was evident for invasive cancer; that is, 73 percent were clinically suspected.

Table 4 compares the casefinding rates reported for first and second screenings in Memphis, Madison, and San Diego. Erickson and his associates reported that of each 1,000 women examined in the first screening, 3.6 were found to have intraepithelial carcinoma and 3.4 invasive cancer of the cervix. In the second screening, of each 1,000 women, 2.2 had intra-

epithelial carcinoma and 0.3 had invasive cancer of the cervix. The investigators suggested that adjustments for age and race differences in the two groups would probably show even greater reductions in casefinding rates. It is reasonable to expect that such adjustments in the Memphis data, and similar adjustments in the data for Madison and San Diego, would help to clarify the relationships between intraepithelial and invasive carcinoma.

Other Research in Cytology

The Cancer Institute's vigorous cytology research program is aimed not only at gathering much needed information on the natural history of uterine cervical cancer, but also at investigating other promising applications of the cytological technique.

A group of institute scientists have described a technique for preparing human whole blood so that it can be examined cytologically for the presence of malignant cells (?). They had previously become aware of the importance of determining whether cancer cells circulate in the peripheral blood of individuals some time before metastasis or generalized spread occurs. Such a finding might be highly valuable in cancer diagnosis or in predicting whether or not an individual cancer would be likely to spread.

Table 4. Comparison of uterine cancer rates in first two examinations

Project and examination	Number examined	Intraepithelial carcinoma		Invasive carcinoma	
		Number	Rate per 1,000	Number	Rate per 1,000
<i>Memphis</i>					
First	108, 136	393	3.6	373	3.4
Second	32, 728	72	2.2	9	.3
<i>Madison</i>					
First	65, 163	206	3.2	335	5.1
Second	9, 111	10	1.1	4	.4
<i>San Diego</i>					
First	33, 746	265	7.8	78	2.3
Second: ¹					
Class 1	9, 109	23	² 1.6	2	.2
Class 2	616	11	² 13.8	0	.0

¹ For second examination, women were classed 1 or 2 according to the results of their first examination. Classes 1 and 2 indicate that the women showed no changes suggestive of cancer in the first examination and that tissue studies were not recommended.

² Adjusted by original author for person-years of experience.

Therefore, the scientists concluded that their method seems to fulfill the requirements of a practical procedure for processing samples of blood containing tumor cells found in individual patients affected with various types of cancer. Further study (8) established that a high percentage of cancer patients have malignant cells that appear to be viable circulating in the bloodstream. The authors noted that their results suggest that examination of peripheral blood may be justified for the establishment of a primary diagnosis of cancer in suspected cases that have eluded diagnosis by other means. The technique may also be of value in following patients after operation to indicate the presence of unsuspected metastases and in determining if manipulation of a tumor at the time of operation actually causes a "spraying" of malignant cells into the bloodstream. Further evaluation of the method is in progress.

Cytology is also being applied toward the detection of cancers of various specific sites other than the cervix, particularly the lung, genitourinary system, and gastrointestinal tract.

Considerable work is being done on the cytoanalyzer (9), an electronic device designed to speed the examination of specimens obtained in the cytological test for uterine cervical cancer. This instrument has been found capable of accurately selecting a significant percentage of specimens that need not be examined further by cytotechnicians or pathologists. Research to improve its operation goes forward steadily. Emphasis is being placed on improving its accuracy and making more of its operations automatic with such developments as a self-focusing device and a mechanical slide feed, now in the research stage. It seems likely that the cytoanalyzer can be modified for use in the examination of cytological specimens obtained from other parts of the body.

Summary

Exfoliative cytology has gained a wide and favorable reputation as a means of detecting cancer of the uterine cervix.

The National Cancer Institute continues a vigorous cytology research program, aimed at gathering information on the natural history of uterine cancer, use of cytology in the study of malignant cells in circulating blood, and perfecting methods of applying cytology to the detection of cancer of other body sites, such as the lung, genitourinary system, and gastrointestinal tract.

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Signs

and

Symptoms

of trends in public health

A project aimed at promoting "more, and less frantic, speech making" was put into effect recently in Iowa. Under a new plan of the State Department of Social Welfare, materials prepared by staff for community interpretation will be swapped between State and county offices on a continuing "circuit" basis. Members of the department who are willing to share public interpretation materials which they have prepared are asked to send them in to the State office for mimeographing and distribution to county departments. The material so disseminated may be used in developing new talks or articles or verbatim, if it fits the occasion and time is pressing.

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Recent acquisitions of literature in the Chinese language at the National Library of Medicine include: photolithographs of ancient medical classics; herbals and collections of prescriptions and formulae for medicinal herb preparations still in common use; works, both ancient and modern, on acupuncture and moxibustion; popular handbooks and guides to basic health rules and practices in hygiene; and monographs on Western medical and pharmaceutical practice.

The relatively high proportion of material in the first and third categories reflects Peking's policy of "rectification of the erroneous attitude of slighting traditional medicine" and strengthening "the unity of traditional and Western style doctors . . . [to] . . . set in motion joint efforts in studying and systematizing traditional medicine" (*Chinese Medical Journal*, 79: 213,

1959). Works written as early as the Han Dynasty (206 B.C. to 220 A.D.) have been reproduced intact in some instances, and in others they have been re-edited, annotated, translated into colloquial language, or clarified through commentaries. The large amount of material on medicinal herbs reflects the intensive effort to domesticate wild herbs for large-scale cultivation to meet current requirements.

Monographs dealing with Western medical practice, aside from translations of English, Russian, and Japanese works, are predominantly basic, clinical discussions of infectious and communicable diseases. Little has been received concerning cancer, heart disease, poliomyelitis, or psychiatric disorders.

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About 87 million Americans have had at least one shot of polio vaccine and 68 million have had three or more injections, according to December estimates by the Public Health Service.

Among persons under 40 years of age, more than 34 million, or almost 30 percent, have had no vaccine. Among children under 5 years of age, the group that accounted for 43 percent of the paralytic cases this year, 4.5 million have had no vaccine.

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Connecticut has amended its public laws to permit special educational training or privileges to emotionally handicapped children (Public Act 664). Previously, this special treatment was confined to children between 4 and 21 years of age with a diagnosed physical or mental handicap.

At the 1960 annual meeting of the Health Physics Society in Boston, Secretary of Health, Education, and Welfare Arthur S. Flemming will speak on the responsibilities and activities of the Federal Radiation Council at a dinner session June 30. The 3-day session, beginning June 29, will also include a symposium on the effects of recommendations of the National Committee on Radiation Protection and Measurements on the interests and activities of labor, law, medicine, and insurance.

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In 91 hospitals in New York City with approved training programs during 1959, 48 percent of the interns and residents were graduates of foreign medical schools. One-fourth of the 9,254 interns and residents in 821 American hospitals were in New York. In 11 of New York's municipal hospitals, not one intern or resident was a graduate of an American school.

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Age and alcohol were significant factors in pedestrian fatalities in New York City in 1959. A study of 50 persons killed by automobiles while walking in Manhattan showed the average age of the victims was 59, one-half were born outside the United States and unmarried, and about three-fourths of those who died within 6 hours after an accident had been drinking. These and other findings of the study conducted by the driver research center of the New York State Department of Health in cooperation with other sponsoring groups were presented at the New England sectional meeting of the American College of Surgeons.

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Forty persons have been hospitalized in Chicago, Ill., for treatment of lead vapor inhalation; all but three were children. After two of the children died, the Chicago Board of Health ordered a wholesale drive against use of discarded storage batteries as fuel in space heaters and furnaces. Police reported four piles of discarded batteries had been found in vacant lots in the southside residential area of the city, where the victims lived.