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The detection of early carcinoma of the cervix

by

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The fact that patients who present with the symptom of abnormal vaginal bleeding may have malignancy of the genital tract has been emphasised. These patients should therefore have urgent and thorough clinical examination and investigation. In this article I would like to consider the detection of early carcinoma of the uterine cervix when the patient usually has no symptoms and even if she were examined, the genital organs may appear normal. It is by means of the relatively young science of vaginal cytology that we are now able to detect the very early forms of carcinoma of the uterine cervix.

The value of vaginal cytology

Since the publication by Papanicolaou and Traut in 1943 of the use of vaginal cytology in the diagnosis of uterine carcinoma, the taking of a "Pap" smear has gradually become established as a clinical test to detect uterine carcinoma. Many gynaecological and obstetric units all over the world began to include the taking of vaginal smears as part of the routine examination of all patients over a certain age, either 20 or 30 years, depending on the facilities available. The Teaching Unit of our hospital with the assistance of Dr. Barter of the King Edward Memorial Hospital, Perth, Australia, began to take vaginal smears on all patients 25 years and above since November 1964.

The basis of vaginal cytology is the fact that malignant cells from the uterus, ovary, fallopian tube and vagina are shed to collect in the posterior vaginal pool. Also, the uterine cervix is an easily accessible organ for the collection of scrape smears. Cells are collected from the posterior fornix, ectocervix and cervical canal on to a glass slide fixed, then stained and examined

TABLE I

Unsuspected Carcinoma Of The Cervix Detected By Cell Smears

Author	No. of Cases	No. of in-situ Carcinomas	No. of invasive Carcinomas
Gynaecological Patients Anderson (1959)	19,464	145 (7.5/1,000)	52
Obstetrical Patients McLaren (1961)	5,000	9 (1.8/1,000)	1
General Practice Patients Macgregor & Baird (1963)	2,683	13 (4.8/1,000)	3
Population Screening Boyes et al (1962)	146,833	828 (5.6/1,000)	87

under a binocular light microscope for the presence of malignant cells. That unsuspected carcinoma of the cervix can be detected by the use of vaginal cytology is evident from Table I. It is readily seen that when cell smears were examined from adult women in a general population or from patients who attend an obstetrical, gynaecological or general practitioner clinic, early carcinoma of the cervix could be detected. These were all unsuspected or preclinical carcinomas of the cervix, carcinoma-in-situ predominantly but a number were occult invasive forms. One would like to emphasise that most of these women were asymptomatic and the cervix when examined might not have suggested having a malignant lesion. The real value of the cytologic method is that it can detect the presence of malignant cells in these patients. If a patient had symptoms suggesting possible malignancy of the genital tract or on clinical examination the cervix looked suspicious, the correct investigation to rely on is biopsy and not a vaginal smear. This is because infection of a carcinomatous lesion may cause degeneration of the cells and result in a false negative smear. This concept is best summarised

NORMAL CERVIX = CYTOLOGY
SUSPICIOUS CERVIX = BIOPSY

Patients in whom malignant cells are found in the vaginal smear are submitted to a cone biopsy of the cervix. This is a removal of a cone of cervical tissue with the base at the portio vaginalis and the apex at the internal os. The reason for the cone biopsy is to diagnose the lesion from which malignant cells have been shed. It is the only method by which the pathologist taking serial sections can confirm the presence of carcinoma-in-situ of the cervix and exclude an invasive lesion. When 1,000 symtomless adult women are screened by the cytologic method, an average of 4 will have positive malignant cells in the vaginal smear. After further investigation by cone biopsy, 3 of these will be found to have carcinoma-in-situ of the cervix and the remaining 1 will have an occult invasive lesion. It must be emphasised that positive cytology is a signal for further investigation by biopsy. It is only after adequate biopsy and knowing the histology of the lesion that definitive treatment can be given. In Fig. 1 is summarised the management of these cases.

The Natural History of Carcinoma of the Cervix

The study of carcinoma-in-situ of the cervix and the use of the cytological method complemented by histological studies have resulted in the theory that the natural history of carcinoma of the cervix may be illustrated as follows.

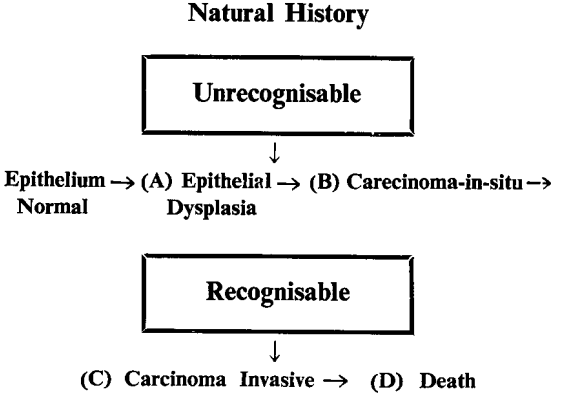
From Fig. 2 it is postulated that the normal cervical epithelium goes through the stage of dysplasia, carcinoma-in-situ and then clinical carcinoma, finally causing the patient's death. Dysplasia and carcinoma-in-situ are unrecognisable clinically. It is known that dysplasia can revert to normal epithelium but whether

FIGURE 1

EARLY CERVICAL CARCINOMA

Management

CARCINOMA-IN-SITU	—(1) RADICAL (Extended Hysterectomy)
	(2) CONSERVATIVE (Cytological Follow-up)
OCCULT INVASIVE CARCINOMA	—(1) RADIOTHERAPY
	(2) WERTHEIM'S HYSTERECTOMY
	(3) RADIOTHERAPY and WERTHEIM'S HYSTERECTOMY



carcinoma-in-situ can do the same is hotly debated, Two other factors that make this diagram not as simple as it looks and therefore the clinical problem not easy of solution are:

1. It is not proven that all clinical carcinoma of the cervix pass through the pre-invasive or in-situ stage. Thus it does not follow that by eliminating all cases of carcinoma-in-situ we can prevent clinical carcinoma of the cervix.

2. It is believed that at least 30% of all cases of carcinoma-in-situ of the cervix become invasive carcinomas in 10—15 years. This is the opinion of Petersen (1955), Lawson (1956), Baird (1963) and Boyes et al (1962). This conclusion was arrived at by the indirect method ofs tatistics and the study of morphology. The truth, however, was stated by Anderson (1959) when he said that "the problem whether carcinoma-in-situ goes on to invasion or not is incapable of solution because diagnosis is always treatment".

Younge (1965) in describing the natural history of carcinoma-in-situ of the cervix referred to a spectrum of progressive changes as shown in Fig. 3.

He has brought in the division of dysplasia into minor and major dysplasia, the latter being sometimes difficult to distinguish from carcinoma-in-situ. Also, pre-clinical carcinoma as shown by Bryans et al (1964) comprise 3 distinct and related entities, carcinoma-in-situ, carcinoma-in-situ with microscopic foci of invasion, and occult invasive carcinoma. The last finally developes into clinical carcinoma of the cervix. Younge is of the ooinion that if the cancer spectrum is stopped at the in-situ stage, then invasive carcinoma of the cervix can be eliminated from a population.

The Prevention of Clinical Carcinoma of the Cervix

Large scale population screening by the cytological method have suggested that prevention of clinical carcinoma of the cervix can be achieved. Bryans et al (1964) conducted a large scale screening programme to detect early cervical cancer among women in British Columbia. They began in 1949 and by 1962 they had screened 381,729 women and estimated that over 50% of the population had by then been screened at least once. Table II shows how the

FIGURE 3

SPECTRUM OF CARCINOMA IN-SITU OF THE CERVIX

DYSPLASIA		PRE-CLINICAL CARCINOMA			CLINICAL CARCINOMA			
					Stage			
Minor	Major	In-situ carcinoma	In-situ with micro-scopic foci of invasion	Occult invasive carcinoma	I	II	III	IV

TABLE II

CASES OF IN SITU CARCINOMA AND PRECLINICAL INVASIVE CARCINOMA DETECTED FROM 1949 TO 1962

YEAR	CASES SCREENED	IN SITU CARCINOMA	IN SITU WITH MICROINVASION	OCCULT INVASIVE CARCINOMA
1949-50	904	9	—	—
1951	2,197	11	1	1
1952	4,140	25	—	2
1953	5,504	28	1	4
1954	8,848	37	4	1
1955	11,707	52	4	2
1956	15,106	77	4	3
1957	18,719	90	7	3
1958	29,875	141	13	7
1959	38,833	143	6	7
1960	58,109	216	9	13
1961	81,614	225	25	13
1962	106,173	296	21	13
TOTALS	381,729	1,350	95	69

number of women screened increased year after year and with this, increasing numbers of pre-clinical carcinomas of the cervix were detected. Bryans et al were able to establish two facts which would seem to justify large scale screening of the population for early carcinoma of the cervix.

Firstly, they were able to deduce from their findings that pre-clinical carcinomas of the cervix, the majority of which were in-situ carcinomas, had a definite relationship to invasive carcinomas. Table III shows the mean ages of patients at various phases in the development of squamous cell carcinoma of the cervix. This suggests a progression of the disease with age. There seems to be a long latent interval of 10—15 years for in-situ carcinoma to become clinically invasive.

Table IV illustrates the morphological aspects of in-situ squamous carcinoma of the cervix in relation to mean age of the patients. It suggests that this lesion grows round the circumference of the cervix and deeper into the glands as the patients grow older.

Secondly, they found that the elimination of large numbers of pre-clinical carcinomas is associated with a drop in the incidence of clinically invasive carcinoma. Table V shows that the incidence of clinically invasive carcinoma of the cervix in the female population of British Columbia has dropped from 28.4 per 100,000 in 1955 to 15.5 per 100,000 in 1962, *i.e.* by 45.5 per cent which is statistically significant.

TABLE III

Mean Age of Patients at Various Phases in the Development of Squamous Cell Carcinoma of Cervix

	Age (yr.)	No. of Patients
Age at onset in cases with previous negative smears	37.7	49
In situ cases	42.3	1,051
In situ with microinvasive foci cases	46.2	73
Microscopically invasive cases	50.4	53
Clinically invasive cases	52.1	569

TABLE IV

Morphological Aspects of In Situ Squamous Carcinoma of Cervix

	No. of Patients	Mean Age (yr.)
Percentage of circumference involved		
25	318	40.8
50	241	41.2
75	100	43.5
100	111	43.9
Depth of extension into glands		
Superficial	462	39.2
Deep	455	44.5

TABLE V

Incidence of Invasive Squamous Carcinoma of the Cervix Uteri in Women over 20 Years of Age in British Columbia in the Years 1955 Through 1962

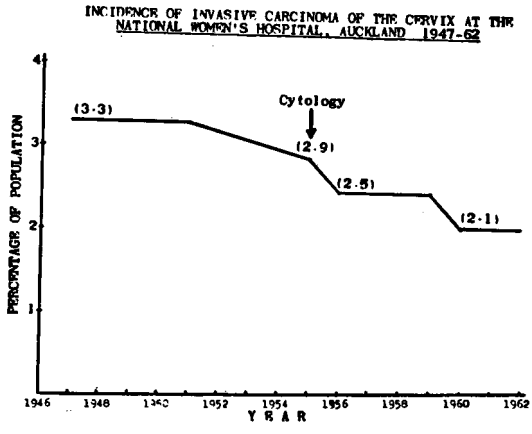
YEAR	POPULATION	CLINICALLY INVASIVE CARCINOMA	
	(in thousands)	Total Cases	Incidence (100,000)
1955	422.9	120	28.4
1956	436.7	119	27.2
1957	460.9	120	26.0
1958	473.0	112	23.7
1959	478.8	108	22.6
1960	486.4	96	19.7
1961	496.0	115	23.2
1962	503·0	78	15.5

In Table VI when the incidence of clinically invasive carcinoma is compared between women who had been screened and those who had not, there is a six to eight fold higher incidence among the unscreened women. Bryans et al have thus shown that large scale screening of women for early carcinoma of the cervix has resulted in a reduction by almost half the incidence of clinically invasive carcinoma in 1962 when compared with that in 1955.

The findings after large scale screening programmes of Christophersen et al (1962) in Jefferson County, Kentucky and Lund (1964) in Munro County, New York, were similar to Bryans et al in British Columbia Their results show that there was a definite reduction in the incidence of clinically invasive carcinoma after several years, and Christopherson found no more invasive carcinoma of the cervix in those screened after 3 years. However, Green (1965) doubts this conclusion as in his experience in the National Women's Hospital, Auckland, there was a fall in the incidence of clinically invasive carcinoma of the cervix even before the introduction of cytology.

He says that this decreasing incidence is a world wide trend. He found (Fig. 4) that in Auckland, the falling incidence of clinically invasive carcinoma of the cervix was not much greater since the introduction of cytology although many more cases of carcinoma-in-situ were being diagnosed and treated. He further contends that carcinoma-in-situ in a fair proportion of cases may be a benign lesion and not a precursor of invasive carcinoma.

Figure 4.



Green thus doubts the conclusion of Boyes et al (1962) in British Columbia that the elimination of pre-clinical carcinomas of the cervix after large scale screening programmes have resulted in the reduction of the incidence of clinical carcinoma of the cervix. In fairness, it must be said that conclusion of workers in British Columbia was arrived at after 14 years

TABLE VI

Incidence of Clinical Invasive Squamous Carcinoma of the Cervix in Women Over 20 Years of Age in British Columbia

	SCREENED			UNSCREENED		
	Women screened to previous year (in thousands)	Clinically invasive carcinoma cases	Rate per 10,000	Women unscreened to previous year (in thousands)	Clinically invasive carcinoma cases	Rate per 100,000
1961	146.8	5	3.4	339.6	110	32.3
1962	201.6	7	3.5	294.0	71	24.1

of scale screening of nearly 400,000 women, while Green in Auckland bases his deduction on the screening of over 100,000 women over 8 years.

If we believe the greater weight of evidence that the detection and treatment of pre-clinical carcinoma of the cervix by the cytologic method can reduce the numbers of clinically invasive carcinomas we must face the disturbing question originally asked in reference to tuberculosis, "If preventable, why not prevented?". Ideally, the whole female population at risk, *i.e.* those between 20 and 60 years old should have an annual vaginal smear performed. This will detect the very early cases of carcinoma of the cervix when adequate treatment can be given and a good prognosis assured. In the State of Singapore, if the 500,000 or so adult women are to be screened once a year, it is estimated that we would require several cancer detection centres with the services of 4 cytologists, 80 cytotechnicians, 12 doctors, 6 nurses, 10 office secretaries and 6 filing clerks. Together with the cost of stationery and laboratory materials it is estimated that it will be about one million dollars per annum, working out to $2 per smear and $500 to pick up a positive case. This compares favourably with the cost in U.K. and in Canada where it costs the equivalent of $3 to perform one smear. Dr. Curtis Lund of New York emphasised that the success of large scale screening programmes both in British Columbia and Munroe County rests on 3 essential factors:—

1. Acceptance and full support in the application of the test by all physicians.
2. Acceptance by patients through lay education.
3. Avoidance of a charge to the patient.

To screen all the female population at risk in Singapore is a gigantic task not easy of achievement. But that must be the goal we should aim for if we believe its usefulness. We can make a start to achieve it if only partially at first. A cytology service will be established in the Kandang Kerbau Hospital in the near future. Those of us who are general practitioners should encourage all women between 20 and 60 years old to have routine cytology performed to detect early carcinoma of the cervix. We can either take the smears ourselves in our own surgery and then send them to the cytology centre for reporting, or channel our patients to attend the cancer detection centre. Those of us who are in hospital practice should include the taking of a vaginal smear as part of the routine investigation of all married women over the age of 20. By so doing we shall begin to prevent the all too familiar sight of advanced carcinoma of the uterine cervix that we meet with today.

References

Bryans, F.E. Boyes, D.A., and Fidler, H.K. (1964): Amer. J. Obstet. Gynec. **88,** 898.

Christophersen, W.M. Parkes, J.E., and Dyre, J.C. (1962): J. Amer. Med. Assn., **182,** 179-82.

Green, G.H. (1965): J. Obstet. Gynaec. Brit. Cwlth **72,** 13, 20.

Lewis, T.L.T. (1964): Progress in clinical obstetrics and gynaecology. 2nd Edition. Churchill Ltd. London. p. 541.

McGregor, J.E., and Baird, D. (1963): Brit. Med. J. **1,** 1631.

McLaren, H.C. (1963): The prevention of cervical cancer. 1st Edition. English Universities Press Ltd. London. p. 93.

Younge, P.A. (1965): J. Obstet. Gynaec. Brit. Cwlth. **72,** 9.