Middle Articles

CONTEMPORARY THEMES

Exfoliative Vaginal Cytology: A Cytohistopathologist's Viewpoint

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"As the World Health Organization said in its report last year, with all the wealth of wisdom that it has at its command: 'Cancer of the cervix is now a preventable disease.'" (Lord Leatherland, 1965). This is a heartening prospect—but, alas, in Britain today the surface of this gigantic exercise in preventive medicine has been little more than scratched and the future is so hazy.

It is probably true that in Britain the inestimable value of cervical cytology is to this day realized and appreciated to its full extent by comparatively few medical men, and the voice of these protagonists crying out for the liberal expansion of cytodiagnostic screening facilities is still in effect but one in the wilderness. Yet it is their conviction that in years to come cytology cancer-screening clinics will be taken for granted as part of our social services, and by this they are sustained and will continue to present their case.

Experience at St. Luke's Hospital

Our experience of cervical and vaginal cytology for cancer detection began at the hospital in January 1960. We struggled on in our laboratory with cytology as a "squeezed-in extra," as most laboratories have had to do and continue to do, until lingering scepticism was swept aside by one particular case which unequivocally impressed upon us the remarkable clinical and diagnostic value of this "new technique."

The case was that of a woman aged 32, social class II-III, symptomless, and under investigation for infertility, whose smears were found to be highly suspicious. The subsequent cone-biopsy revealed an early invasive squamous carcinoma (microcarcinoma) with pre-invasive malignant dysplastic changes in the adjacent epithelium; and this in a cervix judged to be healthy on inspection by an experienced senior gynaecologist. This lesson had a profound effect upon us and dispelled all doubts.

It is unfortunate that during the past few years the urgent need for a nation-wide comprehensive cytodiagnostic service has so often been presented, in the medical and lay press, in a way suggesting that the early detection and prevention of cervical cancer can be achieved easily by the application of "a simple test." The public and some members of the profession are, not surprisingly, becoming bewildered by the seemingly anomalous failure of the medical authorities to make this simple test available to all women "at risk."

The taking of the cervical smear is a simple, painless procedure, but this is not the test. The cytologist has subsequently to examine the smear and form an opinion after studying the morphology of cells and nuclei, and this may take him only a few minutes or as long as an hour or more

if, for example, earlier smears and/or histological sections have to be reviewed. "Test" is in fact a misnomer and should read "expert opinion."

The nature of the cytologist's work and that of his report are insufficiently appreciated. With the ever-increasing pressure of work on hospital laboratories, the somewhat unique technical difficulties and subtle problems inherent in the development and expansion of a cytology service, especially within the framework of the National Health Service, continue slowly to reveal themselves, and it is the purpose of this paper to comment upon these in the light of our own experience.

Smears from over 1,000 cases a month are now being examined in this laboratory from hospitals, local health

ST. LUKE'S HOSPITALS BRADFORD		GYNAECOLOGICAL CYTOLOGY REQUEST FORM		LAB. REF. No.
IMPORTANT				
VAGINAL CYTOLOGY SHOULD BE USED ONLY AS A DIAGNOSTIC AID. THE ULCERATED SURFACE OF A CLINICALLY OBVIOUS CARCINOMA MAY YIELD UNSATISFACTORY SMEARS. ITS USE IS PRIMARILY FOR THE DETECTION OF EARLY SQUAMOUS CERVICAL CARCINOMA. IT MAY FAIL TO DETECT ADENOCARCINOMA OF THE UTERUS AND IT DOES NOT REPLACE DIAGNOSTIC CURETTAGE IN IRREGULAR OR ABNORMAL UTERINE BLEEDING WHEN MALIGNANCY IS CONSIDERED TO BE A POSSIBILITY.				
HOSPITAL/CLINIC		WARD	CONSULTANT	
SURNAME	Hospital/Clinic No.		SLIDE GRADING	
CHRISTIAN NAME	Date of Birth		0 UNSATISFACTORY SMEAR	
Address			1 NORMAL CELLS ONLY	
			2 ATYPICAL INFECTION DUE TO METAPLASIA	
			3 ABNORMAL BUT NOT OBVIOUSLY MALIGNANT	
			4 CELLS SUGGESTING MALIGNANCY	
			5 CELLS CONCLUSIVELY MALIGNANT	
CLINICAL FINDINGS (PLEASE INDICATE BY TICK AS FOLLOWS):—			"OESTRONE" GRADING	
FIRST APPEARANCE / REPEAT / FOLLOW-UP			A INCREASED	
PRESENTING SYMPTOM:			B NORMAL	
CERVIX:			C SLIGHT REDUCTION	
NORMAL / ERODED / SUSPICIOUS / MALIGNANT			D IMPAIRED	
MENSTRUAL CYCLE OR BLEEDING:			E GROSSLY IMPAIRED	
REGULAR / IRREGULAR / MENOPAUSAL / POST-MENOPAUSAL			Normal	
L.M.P.			Neutrophils Slight Increase	
OTHER FINDINGS OR COMMENT			Purulent	
			TRICHOMONADS	
			Monilia Cells with Hyphae	
			Albicans Cells only	
			COMMENT:	
DATE			SIGNATURE	
			DATE	
			PATHOLOGIST	
COLLECTION OF MATERIAL				
NOTE				
PREPARE ONE SMEAR FROM CERVIX, MARK THIS SLIDE 'A' USING LEAD PENCIL, AND TWO FROM VAGINAL POOL. AFTER SMEARING PLACE SLIDE IMMEDIATELY, WHILE STILL MOIST, IN FIXATIVE.				
SMEARS MUST NOT BE ALLOWED TO DRY BEFORE FIXATION				

FIG. 1.—Cytology Request Form. This is in triplicate with carbon interleaves. For hospital cases one Ayre and one pool smear are stained (Papanicolaou) and examined, and the second pool smear is stained (Gram) for monilia. For population-screening the examination is based on the Ayre smear. Address and date of birth are requested to facilitate identification and documentation.

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authority well-women clinics, and family-planning clinics in the Bradford-Keighley-Skipton area (total female population about 300,000).

The intake of smears, other than from hospitals, is restricted. One Ayre and two pool smears per patient are submitted for examination and are accompanied by our cytology request form (Fig. 1).

Technical Difficulties

The practising cytohistologist feels, justifiably, that it is his prerogative to be able to comprehend fully the return of the technical difficulties involved in expanding an effective cytology service, and especially a population-screening programme, and to guess at how gigantic the project, with all its ramifications, could become.

"Cytodiagnosis" training centres for technicians and pathologists have been established, but training courses can serve as little more than an introduction to this subject. To play a significant part in expanding a national cytology service, trained personnel should subsequently either work as members of an already established and experienced cytology laboratory, or return to their own laboratories to pursue their cytological studies only if provision has been made for them to be substantially relieved of former responsibilities and duties by the appointment of additional staff.

As we gain experience the realization is forced upon us, woefully and despairingly perhaps at times, that for experience measured in years there can be no substitute.

Who Should Examine the Smear?

Failure to decide this question, and then to implement the decision, is probably one of the major factors retarding the advancement of a comprehensive cytology service. There are today advocates for the employment of schoolgirls (G.C.E. "O" level biology), laboratory technicians (grade unspecified), married female doctors or retired doctors for part-time work, trained personnel without any previous laboratory or medical experience ("housewife cytologists"), and science graduates. The variety here shown exposes the confusion and indecision.

I suggest that planned expansion of the service should be based upon regional or subregional cytology laboratories (with an implied centralization of administrative control), each with a nucleus of technical staff comprising a technician-in-charge (Grade Chief II) and four or more technicians (Grade Chief I), all to be employed full-time.

Experience and accuracy, not only of individuals but of the laboratory as a whole, are fundamental to this service, and this demands continuity of work through continuity of staff. Without this prerequisite it is difficult to imagine how a reliable full-scale cytology service could evolve and survive.

The experienced staff of a laboratory should work as a team and refer from the one to the other suspicious, difficult, and positive smears. This would enhance the value of the report issued and ease the strain on the individual cytologist.

Correlation of Cytology and Histology

Training and experience in cytology go hand-in-hand with the study of the related histological biopsy material. For measuring the efficiency and accuracy of a cytology laboratory there is no alternative to very close correlation between these two subjects.

A cone-biopsy is, in this hospital, sent to the laboratory unfixed. It is slit open, flattened out on cotton-wool, and hardened and fixed overnight in formol-corrosive solution.

Next morning it is cut into blocks (on average 15–20) about 1 mm. thick by a razor-sharp knife, processed, and stained the following day. In most cases the correct histological diagnosis can be made in the first sections cut from these blocks. If the lesion is pre-invasive, however, the blocks are cut at two or three deeper levels to exclude "invasion." But if the first sections from the blocks are negative when the cytology has been reported positive, then the blocks are sectioned serially. This may be necessitated, for example, when a surgeon has been too vigorous with his pre-operative swabbing of the vagina and cervix, for this trauma can easily detach and strip from the cervical surface the important epithelium at the squamo-columnar junction.

Can a histologist examining a cone-biopsy in another laboratory, possibly unaware of the exact cytological grading and perhaps not very interested, be expected, in every case, to proceed with the thoroughness demanded?

In the planning of a comprehensive cytology service in Britain provision for this correlation should be made. This is the keystone for the success of cervical cytology as a cancer-preventive discipline. To facilitate this correlation and enable the cytology-histology sequence to be seen at a glance we have devised a surveillance chart (Fig. 2). Upon this all

FIG. 2.—Surveillance chart. Fitted to the wall as a dropleaf, this fulfils its purpose more effectively than a bound-volume register.

cases with smears "Grade 3 or higher" are entered. Entries are made of the subsequent histology reports and the chart is periodically surveyed.

Hospital Cytology as Opposed to Population Screening

The proper use and clinical application of vaginal cytology demands a working understanding between clinician and cytologist, mainly in respect of the interpretation of the cytological grading of smears. The need is also partly dictated by the difference in reliability of detection by cytodiagnostic techniques of the two common types of uterine cancer—squamous carcinoma and adenocarcinoma. With squamous carcinoma of the cervix mistakes should be few, or even absent, when Ayre smears properly taken are submitted for examination; but with adenocarcinoma greater difficulties are encountered.

Some cases of adenocarcinoma yield unmistakably positive smears, while in others suspicious or malignant cells may be recognized on review of the smears only after diagnosis has been made by uterine curettage. In 1964 and 1965, at St. Luke's Hospital, only 62% and 69% respectively of the uterine adenocarcinomas were suspected cytologically prior to diagnosis by uterine curettage, whereas for squamous carci-

noma 91% and 95% of the cases respectively were reported "Grade 3 or higher" prior to surgical biopsy (see Table).

The ratio of squamous carcinoma to adenocarcinoma of the body is said to be about two to one (*B.M.J.*, 1966; *Lancet*, 1966), and this is seen to be so in our series (Fig. 3). This

FIG. 3.—Incidence and age distribution of uterine cancer at St. Luke's Hospital, Bradford, during 1964 and 1965. This illustrates the fallacy of the age group 35-60 for screening purposes recommended by the Ministry of Health. Apart from the detection of pre-invasive squamous carcinomas a significant number of the invasive squamous carcinomas and adenocarcinomas outside the age group 35-60 were detected by cytology when clinical suspicion was minimal or absent. The increased incidence of uterine cancer seen in 1965 is almost certainly due to the increasing use of cytology in Bradford.

substantial incidence of adenocarcinoma is of added significance when one remembers that cervical cytology is being advertised as a means of detection of cervical squamous carcinoma.

Malignant smears with appearances suggesting an origin in squamous carcinoma can, surprisingly, be found to be from an adenocarcinoma, and vice versa. The cytologist cannot simply dismiss adenocarcinoma from his field of study, for he can sometimes diagnose it when the clinician has little cause to suspect it. Its early diagnosis affects the patient's prognosis, and the implications of its diagnosis, or otherwise, in a population-screening campaign are obvious.

In hospital the cytologist is entitled to feel that he is sharing with the clinician a responsibility towards the patient and to think that his report will be interpreted by the clinician in conjunction with his findings and the known facts of the case. He assumes that the patient has been examined clinically, that the cervix has been visualized, and that, in the

appropriate case, the possibility of adenocarcinoma and the need for uterine curettage have been considered.

This latter assumption cannot always be made with smears from other sources, when they may perhaps have been taken by individuals with little gynaecological experience or perhaps even by the patient herself by means of a cytopipette, a method with limited value (*MacGregor et al.*, 1966; *Anderson and Clark*, 1966). In these cases the cytologist feels a greater responsibility, as the subsequent disposal of the patient may well be biased by a negative report.

In difficult or doubtful cases repeating smears can be of great value, for the malignant-cell content of positive smears obtained at different times from the same case can vary considerably. For the patient in hospital or attending a hospital clinic this usually presents no problem, but the deliberate recall of a woman to a screening-clinic for repeat smears will in many cases arouse anxiety and fear. This emphasizes the need for smears (a) to be correctly taken on the patient's first visit to the screening-clinic, and (b) to be examined by experienced laboratory staff.

An opinion that all is well when smears are reported negative should be gauged as a probability rather than a certainty.

Considerations such as these emphasize the necessity for experience in this work, and to embark upon a population-screening programme with a staff "trained" but inexperienced is to court disaster.

Who Takes the Smear?

This question will almost certainly for long remain a matter of dispute. Smears, however, taken ad lib. by general practitioners, by gynaecologists and obstetricians at hospital clinics, and by medical officers at family-planning clinics, special (venereal disease) clinics, and local health authority well-women clinics could never be coped with. Laboratories will never be able to deal with unlimited and unrestricted smears.

It is reasonable that smears should be taken routinely when a patient attends a hospital gynaecology clinic. Otherwise, our aim, generally speaking and allowing for the special case and circumstance, should be a co-ordinated system whereby one smear per woman could be offered every three years, and so organized that this objective would be achieved most efficiently and most economically of time, labour, and cost.

It would seem that for population-screening in the immediate future efficiently run local health authority clinics with the necessary medical, nursing, and clerical staff would yield the best results.

It is desirable, I think, that smears should be collected at as few "centres" as possible. Personal contact and under-

Diagnosis by Cytology of the Two Types of Uterine Cancer (St. Luke's Hospital, Bradford), 1964 and 1965

	1964						1965					
	Adenocarcinoma			Squamous Carcinoma			Adenocarcinoma			Squamous Carcinoma		
Total No. of cases	31			57			39			81		
No. with pre-operative cytology	21			47			26			64		
	No. of Cases	%	Cytology Grading	%	No. of Cases	%	No. of Cases	%	Cytology Grading	%	No. of Cases	%
Note. Interpretation: Grade 3: "Alert" or "suspect"; signifies, e.g., repeat, or possible adenocarcinoma Grade 4 or 5: "positive"	0	0	0	2.1	1	0	0	0	0	3.1	2	3.1
	8	38.1	1 or 2	6.5	3	8	30.8	1 or 2	0	0	0	0
	0	0	2-3	0	0	0	0	2-3	1.6	1	1	1.6
	1	4.8	3	2.1	1	4	15.3	3	4.7	3	3	4.7
	4	19.0	3-4	8.6	4	0	0	3-4	10.8	7	7	10.8
	3	14.3	4	31.9	15	5	19.2	4	12.6	8	8	12.6
	4	19.0	4-5	36.1	17	7	27.0	4-5	31.2	20	20	31.2
	1	4.8	5	12.7	6	2	7.7	5	36.0	23	23	36.0
	Total			47			26			64		

standing between laboratory and clinic personnel would then be more intimate, and a better, more consistent standard of smear-collecting would probably be maintained (an important consideration), and problems of documentation (these are quite formidable) be simplified.

We not infrequently see from patients' laboratory record cards that smears have been taken on two or more occasions within 12 months at different clinics. Unless women are told at the time of a gynaecological or obstetrical examination that smears have been taken they may not realize this.

In an endeavour to prevent multiplication of our work, and to ensure that the patient has been informed, we have introduced the use of personal cytology record cards.

Where Should the Line be Drawn?

For patients referred to hospital gynaecology or obstetric clinics we report on a number of items (see Fig. 1). Trichomoniasis can be diagnosed easily by means of the Papanicolaou smear, and the degree of accuracy is high (Oller, 1965). For the diagnosis of moniliasis the second pool smear is stained by Gram's method.

It would be regrettable if women with these infections were in the future allowed to pass through cancer-screening clinics with the infections remaining undiagnosed, as in many cases it would be the discharge which had prompted them to attend. Moreover, we know that the lack of vaginal hygiene may possibly play some part in the aetiology of cervical cancer (B.M.J., 1965).

The diagnosis of these common vaginal infections by "smears" we have found to be greatly appreciated, but unfortunately there is a tendency for the cancer-screening facilities of the laboratory to be used for this "other purpose." The frequency of smear-taking then becomes virtually impossible to control, and embarrassingly, the cytology laboratory finds itself serving a dual purpose.

Population-screening: Who Should be Smeared, and How Frequently?

As facilities expand should our energies be directed towards the higher-risk group (lower social class and high parity), whether they wish to be examined or not? A successful domiciliary service selecting the higher-risk group has been described by Osborn and Leyshon (1966).

Should the service develop essentially as one freely publicized and offering facilities to the women who seek them? Either approach to this problem has its pros and cons, and the pattern of development of the service in different areas must inevitably rest with the individual authorities.

The recommendation of the Ministry of Health for population screening refers to the age group 35–60 with examinations repeated at five-yearly intervals (Ministry of Health, 1965). It is probably the opinion of the majority of gynaecologists and cytologists that 35 is much too high an age limit to set and that 25 would seem more rational (Wilson, 1965); this is supported by a glance at the incidence of cervical cancer at St. Luke's Hospital during 1964 and 1965 (Fig. 3), assuming an "incubation period" for invasive cancer of 5 to 10 years. The "starting-age" of 25 is also supported by the findings of Osborn and Leyshon (1966) and by the review of work done in Edinburgh since 1948 (Anderson, 1965). The upper age

limit of 60 is equally open to criticism. A starting-age of 35 for screening purposes cannot be justified other than on economic grounds.

The recommendation of a five-yearly interval between screening examinations can also be criticized on the grounds that this is too long an interval of time simply because it places too great reliance upon the collection of a single Ayre smear, upon the cytologist's judgement and report based on one examination, and upon the overall efficiency of a screening service. A three-yearly interval would be more realistic and would provide a greater "margin of safety" for all concerned—cytologist, clinician, and patient.

The Future

Technical difficulties and obstacles abound, restricting the immediate rapid expansion of a full-scale nation-wide screening-service, and not the least of the obstacles to be surmounted has been lack of money (McInroy, 1964, 1965). The solving of the problem of financing this programme (it will cost several millions annually) is not the mission of the professional pathologist, but the assurance is comforting that, "The cost of this service is not very great and should not prove a major difficulty" (Lord Champion, 1965).

The onus therefore is now on the medical profession (within the National Health Service is implied) to educate people in the light of modern knowledge and by all the means at its disposal, and to oust from within its own ranks the die-hards in opposition; the onus, too, is on the laboratory cytology service to do its work (the heavy end of the stick), and on the Government to provide the means without undue administrative complexities.

The full realization of these objectives is, alas, destined to take years. By the very nature and magnitude of the undertaking no quick, cheap, and easy short cut is in sight. How many years will pass is a matter for conjecture, but that they will do so and claim their annual toll of victims we can be assured. Humanity, however, will not be unobservant and will one day pass judgement.

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