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EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF CANCER

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The diagnosis of cancer by means of exfoliative cytology is based on the fact that malignant cells exfoliate more readily than their benign prototypes, and also on certain characteristics which these exfoliated malignant cells possess. In some cases these characteristics are so well marked that there is little doubt about the diagnosis; in many other cases however all that can be said of them is that their appearance is suggestive of malignancy. Even a doubtful report is useful because it indicates the need for further investigation by smears or biopsy. With increasing experience of the method comes an increasing number of definite reports both positive and negative, but even the most experienced cytologists are sometimes in doubt.

Cancer cells have been described by many writers (Papanicolaou, Graham, Farber, and others) but never more clearly than by Dudgeon, of St. Thomas's Hospital, London, who in 1934 wrote: 'Malignant cells stain more deeply than their benign prototypes. This is due to the fact that their nuclei have a greater affinity for haemalum. They vary in size and shape, they are larger than normal, and their position relative to the surrounding cytoplasm is in no way constant. The nuclear chromatin is arranged in thick irregular deeply-staining bundles and the fine reticular arrangement of normal cells is rarely seen. The nucleoli are larger than normal, they are sometimes multiple and stand out as prominent pink dots in the sphere of the nucleus'.¹ But no verbal description of malignant cells is adequate. Even good coloured photographs often leave much to be desired. They draw attention to certain features and in this way they are very helpful, but often it is necessary when examining malignant cells to focus up and down in order to get a proper appreciation of the cell. The information obtained in this way obviously cannot be portrayed by a microphotograph.

As a diagnostic method exfoliative cytology lends itself particularly to the diagnosis of cancer of the lung and cancer of the cervix. Its value in regard to other organs has yet to be critically assessed; Work on the subject is proceeding.

Cancer of the Lung

In cancer of the lung a proportion (20-25%) of the growths is beyond the view of the bronchoscopist and it is in these

cases that the method finds its greatest use. It is little bother for even a very sick patient to provide the necessary sputum. Too often, however, saliva is submitted instead of sputum. It should be impressed upon the nurse, or whoever is collecting the specimen, that what is required is a deep cough sputum. It is wise to ask the patient first to swallow his saliva in order to avoid diluting the sputum. This also serves to remind both patient and attendant that it is the secretion from deep down in the lungs which is required. With patience a satisfactory specimen can be obtained in the vast majority of cases. Specimens showing the presence of blood are likely to be most helpful.

The sputum should be examined carefully, and as soon as possible, by the naked eye. This is best done by transferring it to a Petri dish. Then, with a loop, between 5 and 10 smears are made. In selecting portions for microscopical examination attention should be paid to blood-stained areas and also to any solid granules which may be seen in the specimen. Food particles which had been retained in the mouth may mislead, but in practice this does not happen often. The smears are fixed immediately while still wet. This may be done by placing the slides in a mixture of equal parts of 95% ethyl alcohol and ether, and then staining them by the Papanicolaou technique. The method preferred in this laboratory, however, is to place the smears in Schaudinn's solution and then stain them by the technique recommended by Dudgeon. In our experience Meyer's haemalum, which is employed in Dudgeon's method, gives the best nuclear definition; furthermore, it makes it possible to compare the cytological findings more easily with the subsequent histological examination. It must be stated, however, that the Papanicolaou method has decided advantages in the study of vaginal smears.

After staining, the preparations are mounted and examined from end to end in the manner of a histological section. Low power (2/3rds) is used, but all suspicious cells are scrutinised under high power (1/6th). A knowledge of the normal, or at least the benign, cells of the part is essential. While attention is mainly directed to the detection of malignant cells the presence of other cell elements is noted. A preponderance of simple squamous cells suggests dilution with saliva, the presence of lung histiocytes indicates that

the specimen did in fact come from 'deep down'. Considerable numbers of red cells may be present, even though blood was not visible grossly; this will provide indirect evidence of (*inter alia*) cancer. Other bodies may occasionally be seen; eg. cysts of *Entamoeba histolytica*, hooks of hydatid (*C. W. Harington*—personal communication) and fungal elements. In some cases the appearance of caseous material will indicate that smears should be stained by the method of Ziehl-Neelsen.

While sputum is the fluid most commonly examined in suspected cases of cancer of the lung, bronchial washings and pleural fluid, if available, sometimes give information of great value. These are centrifuged and smears prepared from the deposit. As with the sputum, the smears are fixed while wet and stained by a prescribed method.

It is not possible precisely to assess the value of this method in the diagnosis of lung cancer. There are two reasons for this. In the first place, it is not known if all cancers of the lung always exfoliate cells. There is evidence that some do not, and also evidence that some do so intermittently. In the second place, much depends upon the experience of the cytologist and the length of time he can allow himself to devote to the case. Nevertheless, while a precise assessment is impossible it can be confidently stated that in cytology we have an exceedingly valuable method for the diagnosis of lung cancer, which may well prove comparable to an examination of the sputum for acid-fast bacilli in the diagnosis of pulmonary tuberculosis. Furthermore, in exfoliative cytology we have a method which may disclose cancer of the lung even before radiological evidence of it is found—in fact, on occasions, even before clinical symptoms appear.

Cancer of the Cervix

The diagnosis of cancer of the cervix by means of exfoliative cytology was introduced by Papanicolaou in 1943 in the United States of America. The method is employed extensively in that country and to a lesser but increasing extent in Great Britain. As the cervix is so accessible to biopsy it had been suggested that a cytological examination of vaginal smears is redundant. There is weight in this argument. Nevertheless, as Bamforth has recently pointed out: 'The great advantage of the cytological method is that many early and unsuspected cases have been brought to light by it in the first place'.² Therein lies sufficient justification for the method. Furthermore, malignant cells originating in the cervix have been discovered in vaginal smears when initial biopsy of the cervix failed to reveal malignant growth. This procedure, therefore, is not a substitute for, but an adjunct to surgical biopsy.

Vaginal smears prepared from fluid in the posterior fornix, together with smears made from scrapings of the cervix,

are fixed in the manner described for sputum. They are then stained and examined in the usual way. There is some doubt whether intra-epithelial carcinoma can be distinguished from invading carcinoma by this method. On this aspect of the subject Bamforth writes: 'I do not think that the cytological changes can indicate with certainty yet whether it is a case of invasive or non-invasive carcinoma; in order to decide this question one must have recourse to biopsy'.³

As in the diagnosis of cancer of the lung, it is not possible to state in precise terms the value of the method; there are many variable and unknowable factors concerned. However, the figures of Graham,⁴ working in Boston, and Anderson *et al.*,⁵ in Edinburgh, leave no doubt that the method is exceedingly valuable in capable hands. Nevertheless, a positive smear diagnosis should not be accepted as final until it has been confirmed by biopsy, which still remains the standard means for the diagnosis of cancer of the cervix.

Cancer of other Organs

While exfoliative cytology finds its greatest usefulness in the diagnosis of cancer of the lung and cancer of the cervix,

TABLE I. CANCERS WHICH LEND THEMSELVES TO DIAGNOSIS BY CYTOLOGY

<i>Organ</i>	<i>Fluid</i>
1. Breast	Discharge from nipple. Breast suckings.
2. Lung	Sputum. Pleural fluid. Bronchial suckings.
3. Cervix	Vaginal smear. Cervical scrapings.
4. Prostate	Prostatic secretion (during prostatic massage).
5. Bladder	Urine.
6. Kidney and Pelvis of Kidney	Urine (ureteric catheter).
7. Stomach	Fasting gastric juice. Gastric washings. Ascitic fluid.
8. Oesophagus	Fasting gastric juice. Oesophageal washings.
9. Colon	Ascitic fluid. Colonic washings.

its application is by no means limited to these organs. Table I shows the cancers in which this method of diagnosis is possible, together with the fluid used in each instance.

At the present time, if cancer is to be cured at all, an early diagnosis is essential. In exfoliative cytology we have a technique which may, and often does, give the earliest indication of malignant growth.

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