(Dublin), to Dr. Brian Pringle and Dr. J. F. Eustace, and to our colleagues in the Moyne Institute, Trinity College, Dublin, for making this study possible. Miss Jane Cooper helped with the computations and Dr. Richard Doll kindly read the text.

REFERENCES

- Acheson, R. M. (1961). *Brit. J. prev. soc. Med.*, **15**, 49.
 — and Acheson, E. D. (1958). *Ibid.*, **12**, 147.
 — Hemmens, W. F., and Jessop, W. J. (1958). *Gerontologia (Basle)*, **2**, 357.
 — and Jessop, W. J. E. (1961). *Ibid.* In press.
 Anderson, J. T., and Keys, A. (1956). *Clin. Chem.*, **2**, 145.
 Bronte-Stewart, B. (1961). *Brit. med. J.*, **1**, 379.
 Dangerfield, W. G., and Smith, E. B. (1955). *J. clin. Path.*, **8**, 132.
 Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., Kagan, A., and Gordon, T. (1959). *Amer. J. publ. Hlth*, **49**, 1349.
 Doll, R., and Hill, A. B. (1956). *Brit. med. J.*, **2**, 1071.
 Gertler, M. M., and White, P. D. (1954). *Coronary Heart Disease in Young Adults*. Harvard University Press, Cambridge, Mass.
 Gofman, J. W., Lindgren, F. T., Strisower, B., de Lalla, O., Glazier, F., and Tamplin, A. (1955). *Geriatrics*, **10**, 349.
 Hammond, E. C., and Horn, D. (1954). *J. Amer. med. Ass.*, **155**, 1316.
 Karvonen, M., Orma, E., Keys, A., Fidanza, F., and Brozek, J. (1959). *Lancet*, **1**, 492.
 Oliver, M. F. (1958). *Scot. med. J.*, **3**, 225.
 Paterson, J. C., Cornish, B. R., and Armstrong, E. C. (1956). *Circulation*, **13**, 224.
 Perrin, M. J., Krut, L. H., and Bronte-Stewart, B. (1961). *Brit. med. J.*, **1**, 387.
 Sackett, G. E. (1925). *J. biol. Chem.*, **64**, 203.
 Thomas, C. B. (1958). *J. chron. Dis.*, **7**, 198.

METHODS OF DIAGNOSING CERVICAL CARCINOMA-IN-SITU

BY

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All gynaecological patients in our unit since 1951 have been screened by the method of exfoliative cytology. Since 1958, with an increase in the number of technicians able to share the microscopical work, we began to screen all antenatal patients, so that we have now some idea of the place of cytology in clinical practice. The basic use of cytological screening is that it leads to a diagnosis of carcinoma-in-situ which is beyond our usual clinical methods; that is to say, speculum examination shows no sign of the disease at routine gynaecological examination (Papanicolaou and Traut, 1943).

Many clinicians would like to search for carcinoma-in-situ, accepting as we do that it is a curable precursor of invasive carcinoma, but they lack funds to pay for the technical help or the time to carry out the painstaking microscopy on which the success of exfoliative cytology rests. On the other hand, there are clinicians who do not yet screen their patients, since they believe that the case for the removal of carcinoma-in-situ and the subsequent reduction in the incidence of invasive carcinoma in the community has yet to be made out. They concede, however, that for the individual woman with carcinoma-in-situ it is best for her to have it cured at once. There is no clinician in this country or elsewhere who has the temerity to watch known carcinoma-in-situ of the cervix for an indefinite period.

We would refer the clinician who is considering the use of cytology to the excellent studies of Ericson *et al.* (1956) in the U.S.A., and to the even more impressive long-term studies in British Columbia by Fidler, Boyes, and Lock (1957). From the Canadian studies it would seem to us that the case for cytology as an obligatory examination is clearly made out, and Boyes and his colleagues in British Columbia can now offer (via 1,100 family doctors) a cytological test at regular intervals to patients without gynaecological symptoms, and at present 22% of sexually mature women have the test regularly (Boyes, 1961, personal communication). A recent survey of the incidence of invasive carcinoma of the cervix in British Columbia shows a fall of 21%, and this reduction is thought to result from the surgical cure of carcinoma-in-situ. Naturally this fall is unlikely to continue to the complete elimination of cervical carcinoma, but, with cytological tests accepted by more and more women, many will be protected from carcinoma by its removal in its "pre"-stage. Moreover, apart from explosive rapidly growing carcinoma, cytology tests should tend to bring the patient with carcinoma for treatment at an earlier and more curable stage; but this is a less important function of cytology.

From our own experience and with the therapeutic experience of Boyes and his colleagues now available, we feel that it must be accepted that nowadays no gynaecological or obstetrical examination is complete without cytology. The financing of a cytology service for women without symptoms must be discussed in each community and by the National Health Service, for cytology is expensive. It is, however, very cheap when compared with the cost of treating carcinoma with its dreadful mortality and morbidity. Apart from hospital patients, intelligent women in possession of the facts will wish to have the protection provided by cytology. Given time and careful propaganda many women who have come to regard the prophylaxis of antenatal care or even poliomyelitis as commonplace will come to accept cytology "as a routine health examination not really much different from an annual visit to the dentist" (McLennan, 1958).

Our Experience with Cytology

We have already reported our experience of the technique in gynaecological practice (McLaren, Taylor, and Attwood, 1956, 1958) and also when applied to special groups such as diabetics (Noble and Attwood, 1958). We can summarize as follows: from routine cytological screening of gynaecological out-patients we expect (a) cervical carcinoma-in-situ in 3 to 4 per 1,000, (b) carcinoma of cervix missed at routine clinical examination in 1 per 1,000, and (c) carcinoma of the corpus not obvious in out-patients—for example, in menorrhagia in the fourth decade—in about 1 per 1,000. In round figures, 1 in every 200 is a "cytological pick-up"—that is, a diagnosis resulting from reassessment of a patient's condition prompted by the finding of cells regarded by a trained technician as sufficiently like cells from carcinoma or carcinoma-in-situ to justify biopsy studies.

Finally, there are a group of cytology findings which are not yet fully understood but which are at present being studied; the label given to these cell smears is "dyskaryosis," where certain nuclear appearances resemble those found in malignancy. We have evidence that patients who produce this type of cell must be

followed up closely and over long periods, and already we have observed dyskaryotic cell smears transformed to "positive," leading to the histological proof of carcinoma-in-situ.

In summary, then, cytology will net a "positive" in at least one out of every 200 out-patients, which we consider is a reasonable score to be set alongside many hours of microscopy with normal findings. The key to the technique is the skilled cyto-technician, who in our unit is a medical technician who carries out this work as part of his or her general duties.

Improving Our Score

The incidence of carcinoma-in-situ apparently varies with race (Scott, 1960) and probably with such factors as age, and the age when married and when pregnant. Our figure of between three and four cases of carcinoma-in-situ of the cervix per 1,000 out-patients is about average in the world literature, but, like all workers in this field, we had a desire to know if this figure represented our maximum, and also if the application of multiple screening techniques might improve our score (or "pick-up" rate). The incidence of carcinoma-in-situ, the absolute figure, will never be known without routine cervical amputation and histological studies carried out in many thousands of women from all levels of society. Accepting this fact, we set out to apply not only the aspiration of cells from the vaginal pool (a test with which we were familiar) but also two further methods known to be effective in revealing carcinoma-in-situ: (1) scraping the cervix with a simple wooden throat spatula after the method of Ayre (1947), and (2) routine biopsy of the squamo-columnar junction of the cervix (Schiller, 1928, 1938; Younge *et al.*, 1949; Younge and Kevorkian, 1959).

Not every cervix can be subjected to biopsy in gynaecological practice, and certainly not in obstetrical practice, without asking too much from patient and staff. At least in our busy out-patient department, without a large staff of assistants and with the need to teach and consult, routine biopsy of all cervices as a screening method for carcinoma-in-situ is not feasible. We therefore limited biopsy to theatre patients prior to operation or minor procedures such as dilatation and curettage.

Comparison of Scrape and Aspiration Tests

Obstetrics (mainly first trimester).—Consecutive antenatal patients, 1,500; (1) positive scrape test—proved carcinoma-in-situ, 4; positive aspiration tests—proved carcinoma-in-situ, 1. To this procedure we add cytology tests marked as "dyskaryotic" or from a clinician's viewpoint "very suspicious," an indication for cone-biopsy of the cervix—namely, (2) scrape test "very suspicious," 2; aspiration test "very suspicious," 0.

Gynaecology.—Consecutive gynaecological out-patients, 4,000; proved carcinoma-in-situ, 13; positive scrape tests, 13; positive vaginal aspiration tests, 9.

At present, therefore, the information obtained from scraping 1,500 pregnant cervices is as follows: carcinoma-in-situ, 4; atypical hyperplasia, 2. In contrast, with aspiration tests alone we should have recorded only one carcinoma-in-situ. The difference cannot, we think, be explained by a failure of technique, for the cytology team responsible, working under the direction of one of us (M.E.A.), is very experienced.

In *gynaecology*, of 13 cases of carcinoma-in-situ diagnosed as a result of positive scrape cytological tests, aspiration alone would have missed four in a series of 4,000 consecutive out-patients.

In neither obstetrics nor gynaecology was there any advantage in applying *both* aspiration and scrape tests, for on no occasion was the aspiration test positive when the scrape test was negative. There was therefore no case for using both tests as suggested by Song *et al.* (1958) in their extensive field surveys carried out in Rhode Island.

Routine Biopsy

Although we have had experience of biopsy of the post-natal cervix (McLaren, 1952), its routine use for the pregnant or gynaecological patient presents formidable difficulties. For the purpose of comparing a small punch biopsy or biopsies with a scrape-smear and with aspiration cytology we subjected a group of 770 anaesthetized women to biopsy just prior to operation. We excluded obvious carcinoma and also patients giving a positive smear, for which our routine practice is immediate cone-biopsy. We used no ancillary aids such as binocular magnification to locate the site of biopsy (Hinselman, 1925; Navratil *et al.*, 1958), but iodine-staining of the glycogen-bearing epithelium of the portio was used as advocated by Schiller and more recently by Paul Younge. Targets for biopsy were: (1) any "raw" areas extending out from the portio, a so-called erosion; (2) any obvious defect in the squamous epithelium of the portio; and (3) any pale area failing to take up iodine-staining. In all, 972 punch biopsies were taken from 769 women, the bulk of them from the squamo-columnar edge of the cervix. A single biopsy was performed in 623, two biopsies were performed in 111, three biopsies in 13, and four biopsies in 22.

The histology was read by one of us (H.C.M.) first of all without and then with full clinical and cytological notes on each case. It is not proposed here to make a detailed report on classification of the histology but simply to answer one question, "Was there any occasion when carcinoma-in-situ was diagnosed by punch biopsies in the presence of a negative cell smear?" The answer was clearly in the negative, so that we concluded from this small pilot study that routine punch biopsy had nothing to add to routine scrape smears taken from the ectocervix.

Comment

The obvious advantage of the scrape test is that it is easy to perform and never causes more than trivial bleeding (a not uncommon result of a punch biopsy). The "geography" of carcinoma-in-situ has been depicted by several workers (Foote and Stewart, 1948; Galvin *et al.*, 1955); from these studies it appears that a single (random) squamo-columnar biopsy of the cervix may well miss carcinoma-in-situ, but that four biopsies around the squamo-columnar junction are likely to be successful. This observation is obviously important, for most of our biopsies were, in fact, single squamo-columnar biopsies. Nevertheless, we had in mind the practicability of routine biopsy of the cervix in our gynaecological practice, having studied with great interest the report on cervical biopsies taken by Younge *et al.* (1949), who were able to collect 131 carcinoma-in-situ specimens before the days of the routine cytology at the Free Hospital for Women in Boston. These authors did not use colposcopy

or colpo-microscopy to locate their biopsies, although the work of Grünberger (1951), Grünberger and Antoine (1956), and Navratil *et al.* (1958) makes it clear that these methods greatly enhance the chance of a biopsy including pathological tissue.

Summary

Aspiration cell-smears were compared with scrape tests and a limited series of cervical biopsies in their ability to reveal the presence of carcinoma-in-situ proved by biopsy. The most effective method is the Ayre scrape-smear, which can be used alone since there is no overlap with either the aspiration technique or biopsy.

We acknowledge the assistance in this study given by our clinical colleagues, M. J. D. Noble and J. B. Comerford. We also wish to acknowledge financial support from the British Empire Cancer Campaign.

REFERENCES

- Ayre, J. E. (1947). *Amer. J. Obstet. Gynec.*, **53**, 609.
 Ericson, C. C., *et al.* (1956). *J. Amer. med. Ass.*, **162**, 167.
 Fidler, H. K., Boyes, D. A., and Lock, D. R. (1957). *J. Canad. med. Ass.*, **77**, 79.
 Foote, F. W., and Stewart, F. W. (1948). *Cancer*, **1**, 431.
 Galvin, G. A., Jones, H. W., and Te Linde (1955). *Amer. J. Obstet. Gynec.*, **70**, 808.
 Grünberger, V. (1951). *Acta gynæc. obstet.*, **1**, 208.
 — and Antoine, T. (1956). *Atlas der Kolpomikroskopie*. Thieme, Stuttgart.
 Hinselman, H. (1925). *Münch. med. Wschr.*, **2**, 1733.
 McLaren, H. C. (1952). *Brit. med. J.*, **1**, 347.
 — (1960). *Acta Un. int. Cancr.*, **16**, 385.
 — Taylor, C. W., and Attwood, M. E. (1956). *J. Obstet. Gynaec. Brit. Emp.*, **63**, 801.
 — (1958). *Lancet*, **1**, 398.
 McLennan, H. R. (1958). Discussion on Cytology, B.M.A. Glasgow Division.
 Navratil, E., Bajardi, F., and Nash, W. (1958). *Amer. J. Obstet. Gynec.*, **75**, 1292.
 Noble, M. J. D., and Attwood, M. E. (1958). *J. Obstet. Gynaec. Brit. Emp.*, **65**, 64.
 Papanicolaou, G. N., and Traut, H. F. (1943). *Diagnosis of Uterine Cancer*. Commonwealth Fund, New York.
 Schiller, W. (1928). *Zbl. Gynäk.*, **52**, 1886.
 — (1938). *Surg. Gynec. Obstet.*, **66**, 129.
 Scott, Agnes (1960). *J. Obstet. Gynaec. Brit. Emp.*, **67**, 832.
 Song, Y. S., Fanger, H., and Murphy, T. (1958). Transactions of Inter-Society Cytology Council, Statler Hotel, N.Y.C., Nov. 13, 1958.
 Younge, P. A., Hertig, A. T., and Armstrong, D. (1949). *Amer. J. Obstet. Gynec.*, **58**, 867.
 — and Kevorkian, A. Y. (1959). *Cancer of the Cervix*, Ciba Foundation Study Group 3. Churchill, London.

The importance of diagnosing impaired hearing in young children at as early an age as possible so that the appropriate medical and educational measures can be instituted has been emphasized in guidance issued jointly by the Ministries of Health and Education to local health and education authorities, hospital authorities, and executive councils. Local authorities are asked to review the adequacy of the methods of finding cases of impaired hearing through their maternity and child welfare and school health services; to consult with local medical committees on arrangements for co-operation with general practitioners to ensure a comprehensive system of early ascertainment; and to examine with hospital authorities and local medical committees the arrangements for babies born in hospital. Children considered to be "at risk" are infants with a family history of deafness, and those known to have been subjected to any adverse pre-natal or perinatal influence; children with congenital abnormalities, multiple handicaps, cerebral palsy, and speech defects; and all retarded children.

ACUTE ALCOHOLIC HEPATITIS

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[WITH SPECIAL PLATE]

"One may drink wine and be nothing the worse for it; on another, wine may have effects so inflammatory as to injure him both in body and mind."—SAMUEL JOHNSON (1776).

Severe jaundice is regarded as an ominous event, indicative of impending death, in the chronic alcoholic patient with cirrhosis. Thus in a series of 386 patients with cirrhosis, 65% of whom were jaundiced at some time, Ratnoff and Patek (1942) found that half of the 168 who died jaundiced did so within two months and 85% within a year of the onset of jaundice: and among the alcoholic cirrhotic patients of Boston reported by Summerskill and his colleagues (1960) 11 out of 18 were deeply jaundiced at death and only 4 out of 35 recovered from severe jaundice.

Severe jaundice may, however, occur in alcoholics at an earlier stage, and before cirrhosis is established, when it is accompanied by marked constitutional disturbances—fever, anorexia, abdominal pain, nausea, and vomiting. The liver is enlarged and tender, and shows histologically acute inflammatory changes in addition to those of any underlying condition. The illness tends to run a protracted course, often ends fatally, but is potentially recoverable with suitable treatment.

Jaundice has long been known to follow alcoholic excesses (French, 1912; Hurst, 1934, 1938, 1941; Bocca, 1936), and earlier writers attributed some cases of "acute necrosis of the liver" to an excess of alcohol (Osler, 1892; Rolleston and McNee, 1929). Few other reports of severe jaundice in alcoholics (Davis and Culpepper, 1948; Welin, 1950; Eckhardt *et al.*, 1950) appeared before the importance of acute hepatic insufficiency in chronic alcoholics was stressed by Phillips and Davidson (1954), all of whose 56 patients had drunk heavily before the jaundice developed. These authors assigned a bad prognosis to the condition, many of their patients dying and the remainder showing varying degrees of slow and mainly incomplete recovery. They described a histological picture which they believed to be characteristic and which will be described later. Of 28 patients with the characteristic lesions, 18 died, as did 10 of 13 with severe jaundice.

The object of the present paper is to emphasize the recognition and treatment of this condition, which have received scant attention in the literature of Great Britain. Seven cases of acute alcoholic hepatitis investigated by the authors at the Royal Free Hospital since 1953 are considered, though other such cases were treated in the hospital during that time.