J. clin. Path., 1976, **29**, 959-966

Adenosquamous carcinoma of the endometrium[1]

M. T. HAQQANI AND H. FOX

From the Department of Pathology, University of Manchester

SYNOPSIS An adenosquamous carcinoma of the endometrium is one which contains both malignant glandular and malignant squamous components; such tumours are considered rare in Britain but are thought to account for nearly one-third of all endometrial neoplasms in the United States. A survey of 675 cases of endometrial cancer seen during the period 1956-75 showed that the incidence of adenosquamous carcinoma was 5%, an incidence that remained static during this 20-year period. The principal difficulties encountered in the diagnosis of these neoplasms are in identifying the squamous component as such and in differentiating it from benign metaplastic squamous epithelium.

The prognosis for patients with an endometrial adenosquamous carcinoma is very much worse than for women with a pure adenocarcinoma, and because these neoplasms are often wrongly identified it is possible that the currently accepted prognoses for both pure adenocarcinoma and adenoacanthoma of the endometrium may have to be revised.

There appears to be a true variation in the incidence of this neoplasm between Britain and the United States.

Adenocarcinoma of the endometrium frequently contains foci of squamous metaplasia; if these are extensive or prominent the tumour is often considered to fall into a separate category of 'adenoacanthoma'. It is widely thought that the prognosis of adenoacanthoma does not differ significantly from that of pure adenocarcinoma, and many workers feel that there may be little justification for regarding the adenoacanthoma as a separate oncological entity (Fox, 1973). Several authors have, however, noted occasional examples of endometrial carcinoma containing squamous tissue which had all the morphological characteristics of malignancy (Skinner and McDonald, 1940; Ayre, 1945; Novak and Nally, 1957; Tweeddale *et al*, 1964; Liu, 1972). Tumours of this type, containing both malignant glandular and malignant squamous tissue and known variously as 'mixed tumours' or 'adenosquamous carcinoma', are generally thought of as being very rare and have received scant attention in this country. It has been claimed, however, that in the United States this form of endometrial neoplasm is becoming increasingly common (Ng, 1968; Silverberg *et al*, 1972; Ng *et al*, 1973), and, indeed, Reagan (1974) has commented that such neoplasms now account for at least one-third of all malignant endometrial tumours. This rising incidence of adenosquamous carcinoma is viewed with concern because it is considered that this form of neoplasm has a very much worse prognosis than does the pure adenocarcinoma of the endometrium (Ng *et al*, 1973).

Because this endometrial neoplasm has been little studied in this country and because we were not aware of seeing these tumours with the frequency with which they are apparently encountered in the United States, we reviewed all cases of endometrial cancer seen at St. Mary's Hospital, Manchester since 1956 in an attempt to determine the incidence of, the diagnostic criteria for, and the prognosis of adenosquamous carcinoma of the endometrium.

Material and methods

The histological sections from all cases of malignant disease of the endometrium seen at St. Mary's Hospital, Manchester between 1956 and 1975 were reviewed; the sections studied included those from the cervix and, where available, the ovaries. Cases of endometrial stromal sarcoma, mixed mesenchymal sarcoma, and malignant lymphoma of the endometrium were excluded as were also those in which a

[1]This paper was read at the 96th General Meeting of the Association of Clinical Pathologists at the University of York, 8-9 April 1976.

co-existent neoplasm was present in the cervix or a concomitant endometrioid adenocarcinoma in the ovary. This left a residue of 675 cases available for review and these were diagnosed as either adenocarcinoma or adenosquamous carcinoma by agreement between two observers; no separate category of adenoacanthoma was recognized, and tumours containing benign metaplastic squamous epithelium of any degree or extent were included within the adenocarcinoma group. Neoplasms were diagnosed as adenosquamous carcinoma only if both observers were completely satisfied that malignant squamous epithelium was admixed with the adenocarcinomatous tissue; where doubt existed the tumour was classed as adenocarcinoma.

The case notes of patients with adenosquamous carcinoma were scrutinized, and an attempt was made to obtain the fullest possible follow-up information. A control series of case notes from 100 patients with endometrial adenocarcinoma was also reviewed; these cases were selected from the files in a totally random fashion from the 20-year period covered by the review; no attempt was made to match the two groups for age or for any other factor.

Results

INCIDENCE

Six hundred and seventy-five malignant endometrial tumours were examined and, of these, 34 were considered to be of the adenosquamous type. The overall incidence of adenosquamous carcinoma over the 20-year period was almost exactly 5% and there was no evidence of any notable increase in this incidence between 1956 and 1975 (table I).

HISTOLOGICAL FEATURES

The diagnostic criterion of an adenosquamous carcinoma was the presence of both malignant glandular and malignant squamous tissue within the same neoplasm (fig 1). The glandular components of these tumours showed all the well-recognized characteristics of adenocarcinoma and did not differ in any way from those seen in pure adenocarcinoma of the endometrium (fig 2); the vast majority of adenosquamous carcinomata contained well-differentiated glandular tissue which in most cases was of the G1 grade, only a minority being of the G2 grade and none being graded G3. In all the cases the adenocarcinomatous element was the predominant feature of the tumour, and in none did it account for less than 70% of the neoplastic tissue.

Years	*Total no. of cases of endometrial cancer*	*Adenosquamous carcinoma*	
		No.	*%*
1956-60	185	9	4·8
1961-65	175	8	4·5
1966-70	146	8	5·4
1971-75	169	9	5·3
1956-75	675	34	5·0

Table I *Incidence of adenosquamous carcinoma of the endometrium 1956-75*

The malignant squamous epithelium (fig 3) sometimes occurred in close proximity to, or even in apposition with, the malignant glandular tissue, but more frequently the two components were separated by connective tissue; there was no true intermingling of squamous and glandular tissues and malignant squamous epithelium was not seen within a glandular lumen; the squamous carcinomatous tissue was not in continuity with glandular epithelium, and transitional forms were not noted. The malignant squamous epithelium was rarely of the frankly keratinizing variety though individual cell keratinization was seen in a moderate proportion of cases; the cells were large, showed a variable degree of pleomorphism and mitotic activity, were polygonal or elongated with indistinct cell boundaries and very few, if any, intercellular bridges, and had relatively abundant, homogenously acidophilic cytoplasm and centrally placed nuclei with irregularly distributed, sometimes pyknotic, chromatin and prominent nucleoli.

In almost one-third of the adenosquamous carcinomata benign metaplastic squamous epithelium was also present. This was recognized, and differentiated from the squamous carcinomatous tissue, by its intraglandular position and the absence of any of the cytological hallmarks of malignancy (fig 4). No evidence was seen of any transition from benign to malignant squamous epithelium.

PROGNOSIS

The crude survival rates for patients with endometrial adenosquamous carcinoma and for those with endometrial adenocarcinoma are shown in table II. Because both series included patients lost to follow-up or followed up for very variable periods of time, a corrected survival rate for each group was calculated using Armitage's (1971) modification of Berkson and Gage's (1950) method; these calculated results are shown in tables III a and b and indicate a very much poorer survival rate for patients with adenosquamous carcinoma.

Discussion

Endometrial neoplasms containing both malignant glandular and squamous tissue have been variously

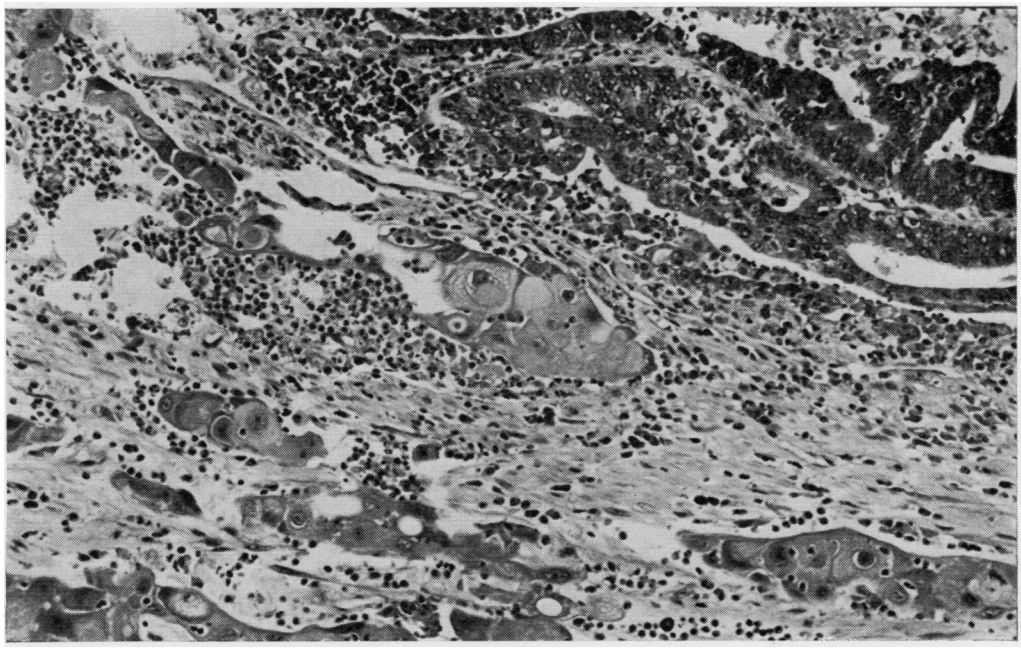

Fig 1 *An endometrial adenosquamous carcinoma. Adenocarcinomatous areas are above and to the right while malignant squamous tissue is seen below and to the left. (H and E × 120)*

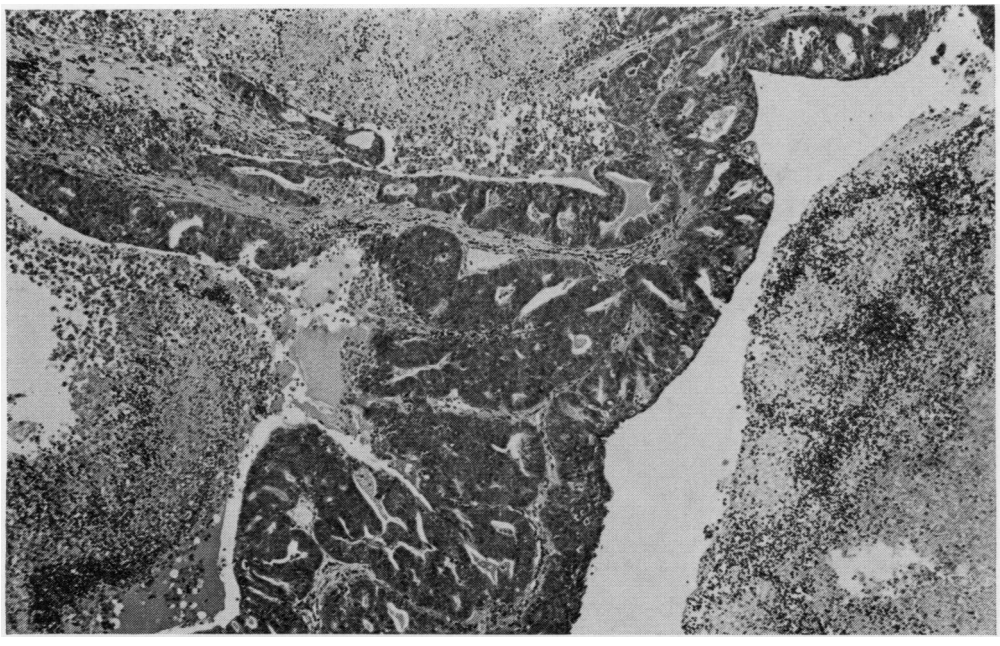

Fig 2 *A different field of the tumour illustrated in fig 1; the appearances are those of an adenocarcinoma. (H and E × 50)*

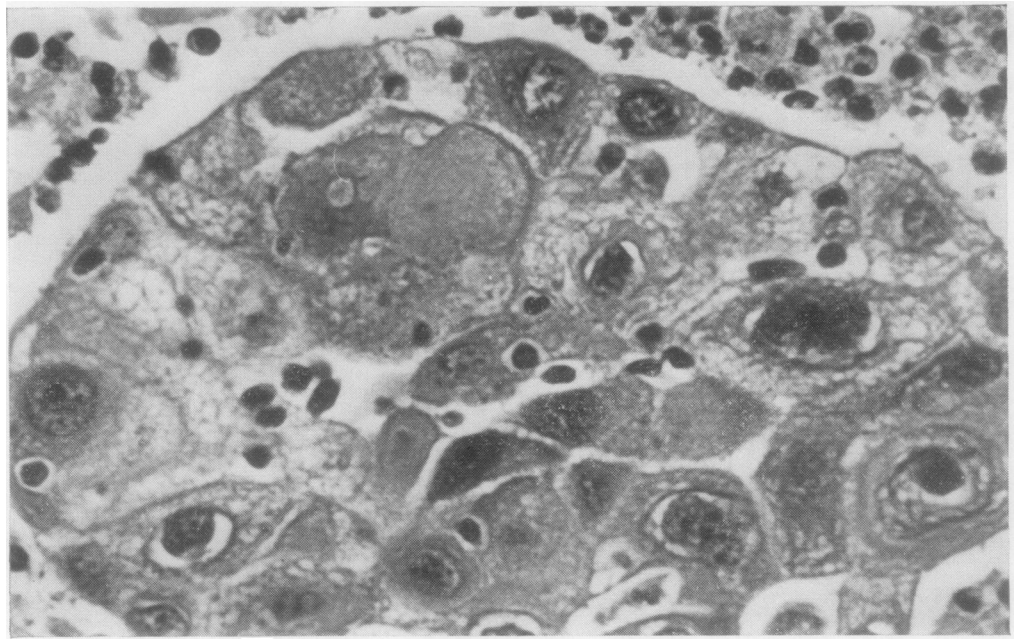

Fig 3 *Malignant squamous tissue in an adenosquamous carcinoma of the endometrium. Unusually, intercellular bridges can be seen. (H and E × 450)*

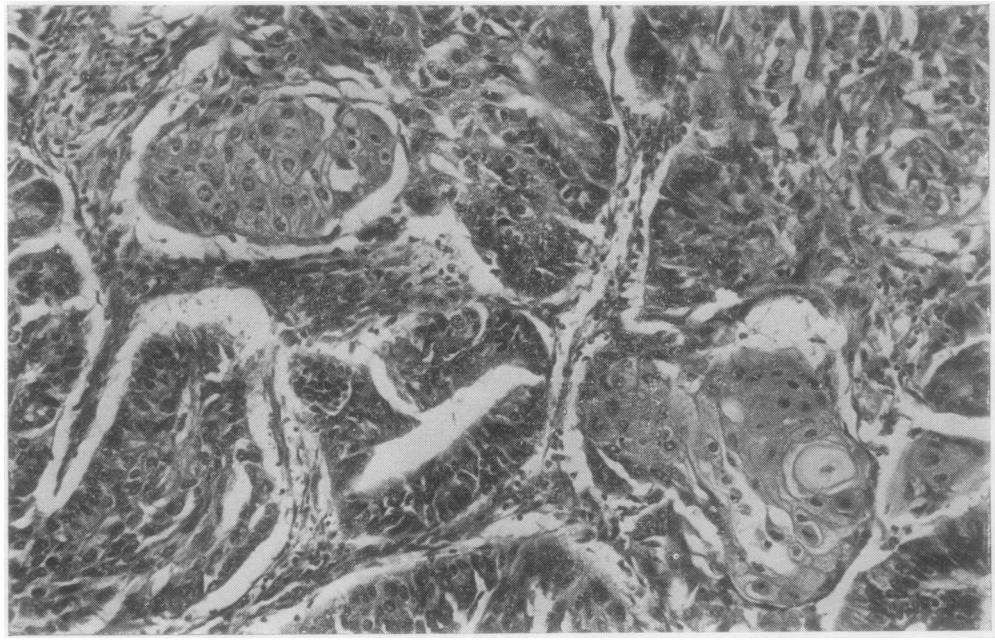

Fig 4 *Benign metaplastic squamous tissue in an endometrial adenoacanthoma. (H and E × 120)*

	Adenocarcinoma	*Adenosquamous carcinoma*
Total number of patients	100	34
No follow-up	13	4
Died of endometrial cancer	13	12
Died of other causes	5	0
No. alive < 5 years	29	6
No. alive at 5 years	40	15
No. alive at 10 years	37	12

Table II *Follow-up of patients with endometrial cancer*

Interval since diagnosis (years)	*Estimated probability of death during this period*	*Estimated probability of survival during this period*	*Estimated percentage of patients alive at end of period*
(a) Endometrial adenocarcinoma			
0-2	0·1198	0·8802	88
2-5	0·0600	0·9400	83
5-10	0	1·0000	83
(b) Endometrial adenosquamous carcinoma			
0-2	0·2413	0·7587	76
2-5	0·1176	0·8824	67
5-10	0·3333	0·6666	45

Table III *Calculated survival rates of patients*

described as 'mixed tumours' or 'adenosquamous carcinoma'. The latter name is preferred, partly because the term 'mixed tumour' is already applied with equal validity to carcinosarcoma and to mixed mesenchymal tumours of the endometrium and partly because it specifically identifies the constituent components.

Although the incidence of adenosquamous carcinoma was much lower in our series than in some recently reported American studies, it nevertheless came as something of a surprise to find on review that one in 20 of our patients was suffering from this form of neoplasm: none of the neoplasms classed by us as adenosquamous carcinoma had previously received this label. A few of the tumours had been categorized simply as adenocarcinoma, not because the squamous elements had been overlooked but because they had been regarded as solid areas of adenocarcinomatous tissue; most had, however, been diagnosed as adenoacanthoma and the squamous component had been considered to be benign and metaplastic rather than neoplastic and malignant.

Previous failure to diagnose these neoplasms was due principally to a lack of sufficient awareness of this oncological entity, but diagnostic problems arise even when a specific search is made. First, the squamous component has to be identified as such; secondly, its malignant nature has to be recognized; and, thirdly, a distinction must be made from a 'collision tumour' in which there is intermingling of an endometrial adenocarcinoma and a cervical squamous-cell carcinoma.

Ng and his colleagues (Ng, 1968; Ng *et al*, 1973) consider that the squamous component of an adenosquamous carcinoma can take any one of three forms: (1) keratinizing large-cell type; (2) non-keratinizing large-cell type; and (3) non-keratinizing small-cell type. If the epithelium is of the large-cell keratinizing type, there is usually little difficulty in recognizing its squamous nature; unfortunately, the presence of this type of epithelium is a feature of only a small minority of adenosquamous carcinomata, most of which contain only non-keratinizing epithelium. The large non-keratinizing cells have been convincingly shown to have the typical ultrastructural characteristics of squamous cells (Aikawa and Ng, 1973), and indeed their nature is often readily apparent on light microscopy; in a high proportion of cases, however, reliance has to be placed upon their large size, polygonal shape, and acidophilic cytoplasm. The small-celled non-keratinizing type of epithelium (fig 5) is not obviously recognizable as squamous on light microscopy, is very difficult to differentiate from anaplastic adenocarcinoma, and has not been studied electronoptically; we feel that its nature has not been firmly established and have not classed tumours as adenosquamous carcinoma if the only non-glandular malignant epithelium present was of the small-cell, non-keratinizing variety.

Often the squamous component of these neoplasms has all the cytological hallmarks of malignancy and is easily distinguished from benign metaplastic squamous tissue. Sometimes the distinction is less obvious, but, in our experience, metaplastic squamous epithelium is usually intraglandular, is in continuity with glandular epithelium, and does not invade the stroma (fig 6); by contrast, malignant squamous epithelium is extraglandular, not in continuity with glandular epithelium, and infiltrates the stroma.

If it is established that the neoplasm contains a malignant squamous component, it cannot be unequivocally accepted as an adenosquamous carcinoma of the endometrium unless the cervix has been examined and shown to be free of tumour.

The importance of recognizing the adenosquamous carcinoma of the endometrium is shown by the marked difference between its prognosis and that of pure adenocarcinoma, for our study confirms that this is a relatively lethal form of endometrial neoplasm. It is indeed possible that, by adopting a somewhat overcautious attitude towards the diagnosis of adenosquamous carcinoma, we have underestimated its killing potentiality for, by insisting on the presence of clearly recognizable

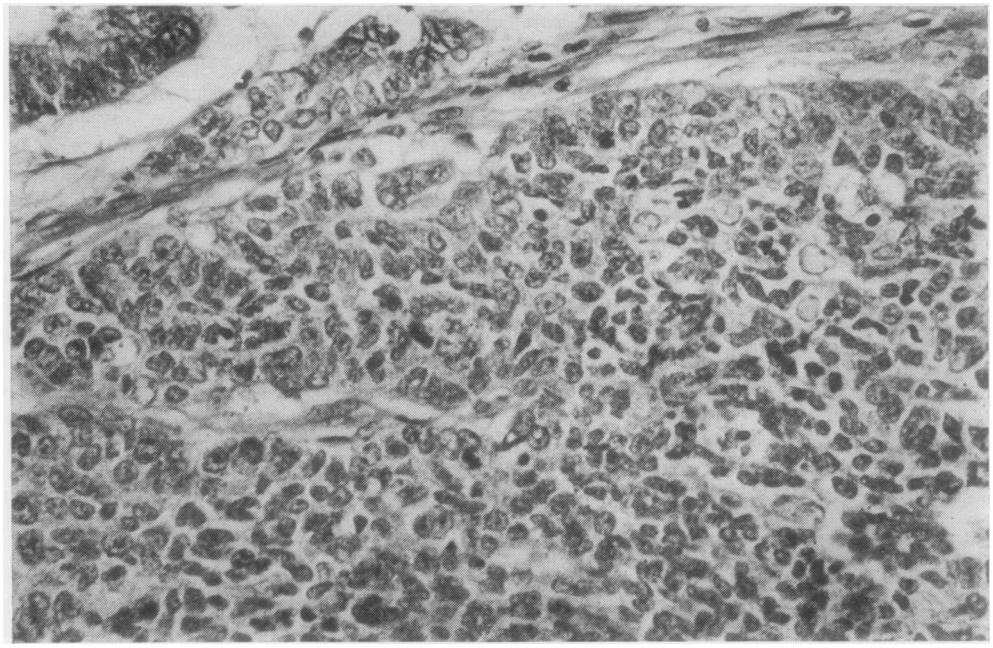

Fig 5 *A small-celled area in an adenocarcinoma. This is not clearly identifiable as squamous in type. (H and E × 300)*

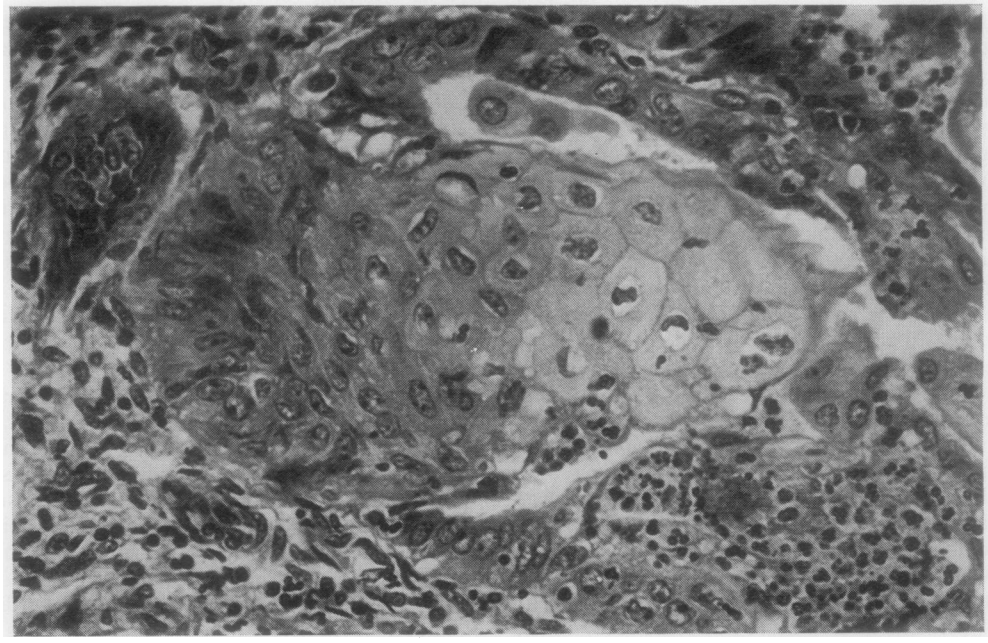

Fig 6 *Benign metaplastic squamous epithelium in an adenocarcinomatous acinus. The squamous epithelium is in continuity with the glandular epithelium. (H and E × 300)*

glandular and squamous components, we have tended to put the least differentiated neoplasms into the adenocarcinoma group; this possible trend to underdiagnosis may have been further accentuated by the exclusion of tumours containing the small-celled non-keratinizing type of epithelium. It is, therefore, not surprising that Silverberg *et al* (1972) calculated an actuarial five-year survival rate for women with endometrial adenosquamous carcinoma of only 35·3% while Ng *et al* (1973) noted that less than 20% of such patients survived for five years.

The reasons for this extremely poor prognosis are not clear. It is not apparently due to the adenosquamous carcinoma being merely less well differentiated than the adenocarcinoma for the very rigidity of our diagnostic criteria meant that in nearly all our cases the glandular element, at any rate, was well differentiated and could be classed as either G1 or G2 in the FIGO grading system. Ng *et al* (1973) commented that adenosquamous carcinoma was usually more advanced at the time of diagnosis than pure adenocarcinoma but this was a factor which, in a retrospective survey of this nature, we were unable to evaluate adequately and is anyway simply another manifestation of the apparently high degree of inherent malignancy which these tumours possess.

The high mortality rate associated with these tumours together with their frequent misdiagnosis implies that the prognosis for pure adenocarcinoma is probably better than is usually realized since many reported series of endometrial adenocarcinoma presumably contain a proportion of these neoplasms, the inclusion of which will influence the overall mortality rate. Furthermore, as adenosquamous carcinoma is often classed as adenoacanthoma, it is possible that the widely held view that adenoacanthoma has exactly the same prognosis as pure adenocarcinoma (Williams, 1965; Morrison, 1966; Charles, 1967; Badib *et al*, 1970; Pokoly, 1970; Fox, 1973) is incorrect. Silverberg *et al* (1972), after excluding cases of adenosquamous carcinoma, noted that adenoacanthoma has a very much better prognosis than pure adenocarcinoma, a conclusion which may be nearer the mark.

Finally, we have to consider the differing incidence of adenosquamous carcinoma in this country and in the United States. The most obvious explanation would be that either we are underdiagnosing these tumours or that there is a tendency to overdiagnose them in the United States. We accept a probable element of underdiagnosis in our series, but even in the study of Ng *et al* (1973) the small-celled non-keratinizing type of epithelium, which we excluded, accounted for only 4·4% of cases and the omission of this sub-variety would not materially alter the observed differences. We doubt that the experienced observers in the United States who have reported these series are guilty of overdiagnosing 25% of their cases and we must therefore accept that a true difference in incidence exists between the two countries. Any explanation for this variation must, at the moment, be entirely speculative, but it is perhaps worthy of note that the use of oestrogens for the treatment of menopausal symptoms has been common practice in the United States for much longer than in Great Britain and that the use of exogenous oestrogens has recently been implicated as a cause of an increased incidence of endometrial neoplasia (Smith *et al*, 1975; Ziel and Finkle, 1975); it is possible that the increase may be largely because of an excess incidence of adenosquamous carcinoma.

References

Aikawa, M. and Ng, A. B. P. (1973). Mixed (adenosquamous) carcinoma of the endometrium: electron microscopic observations. *Cancer (Philad.)*, **31**, 385-397.

Armitage, P. (1971). *Statistical Methods in Medical Research*. Blackwell, Oxford.

Ayre, J. E. (1945). Adenoacanthoma of uterus. *Amer. J. Obstet. Gynec.*, **49**, 261-264.

Badib, A. O., Kurohara, S. S., Vongtama, V. Y., Selim, M. A., and Webster, J. H. (1970). Biologic behaviour of adenoacanthoma of endometrium. *Amer. J. Obstet. Gynec.*, **106**, 205-209.

Berkson, J. and Gage, R. P. (1950). Calculation of survival rates for cancer. *Mayo Clin. Proc.*, **25**, 270-286.

Charles, D. (1967). Endometrial adenoacanthoma: a clinicopathological study of 55 cases. *Cancer (Philad.)*, **18**, 737-750.

Fox, H. (1973). The normal and abnormal endometrium. In *Postgraduate Obstetrical and Gynaecological Pathology*, edited by H. Fox and F. A. Langley, pp. 115-146. Pergamon Press, Oxford.

Liu, C. T. (1972). A study of endometrial adenocarcinoma with emphasis on morphologically variant types. *Amer. J. clin. Path.*, **57**, 562-573.

Morrison, D. L. (1966). Adenoacanthoma of the uterine body. *J. Obstet. Gynaec. Brit. Cwlth*, **73**, 605-610.

Ng, A. B. P. (1968). Mixed carcinoma of the endometrium. *Amer. J. Obstet. Gynec.*, **102**, 506-515.

Ng, A. B. P., Reagan, J. W., Storaasli, J. P., and Wentz, W. B. (1973). Mixed adenosquamous carcinoma of the endometrium. *Amer. J. clin. Path.*, **59**, 765-781.

Novak, E. R. and Nally, W. B. (1957). Uterine adenoacanthoma. *Obstet. and Gynec.*, **9**, 396-402.

Pokoly, T. (1970). A comparison of the clinical behaviour of uterine adenocarcinomas and adenoacanthomas. *Amer. J. Obstet. Gynec.*, **108**, 1080-1084.

Reagan, J. W. (1974). Cellular pathology and uterine cancer. *Amer. J. clin. Path.*, **62**, 150-164.

Silverberg, S. G., Bolin, M. G., and DeGiorgi, L. S. (1972). Adenoacanthoma and mixed adenosquamous carcinoma of the endometrium: a clinicopathologic study. *Cancer (Philad.)*, **30**, 1307-1314.

Skinner, I. C. and McDonald, J. R. (1940). Mixed adenocarcinoma and squamous cell carcinoma of the uterus. *Amer. J. Obstet. Gynec.*, **40**, 258-266.

Smith, D. C., Prentice, R., Thompson, D. J., and Herrmann, W. L. (1975). Association of exogenous estrogen and endometrial carcinoma. *New Engl. J. Med.*, **293**, 1164-1167.

Tweeddale, D. N., Early, L. S., and Goodsitt, E. S. (1964). Endometrial adenoacanthoma: a clinical and pathologic analysis of 82 cases, with observations on histogenesis. *Obstet. and Gynec.*, **23**, 611-619.
Williams, G. L. (1965). Adenoacanthoma of the corpus uteri. *J. Obstet. Gynaec. Brit. Cwlth*, **72**, 674-676.
Ziel, H. K. and Finkle, W. D. (1975). Increased risk of endometrial carcinoma among users of conjugated estrogens. *New Engl. J. Med.*, **293**, 1167-1170.

Reports and Bulletins prepared by the Association of Clinical Biochemists

The following reports and bulletins are published by the Association of Clinical Biochemists. They may be obtained from The Publishing Department, British Medical Journal (ACB Technical Bulletins), B.M.A. House, Tavistock Square, London WC1H 9JR. Overseas readers should remit by British Postal or Money Order.

SCIENTIFIC REPORTS (price £1·00/$2.00 each)

3 Automatic Dispensing Pipettes: an assessment of 35 commercial instruments September 1967 P. M. G. BROUGHTON, A. H. GOWENLOCK, G. M. WIDDOWSON, and K. A. AHLQUIST

4 An Evaluation of five Commercial Flame Photometers suitable for the Simultaneous Determination of Sodium and Potassium March 1970 P. M. G. BROUGHTON and J. B. DAWSON

SCIENTIFIC REVIEWS (price £1·00/$2.00 each)

1 The Assessment of Thyroid Function March 1971 F. V. FLYNN and J. R. HOBBS

2 Renal Function Tests Suitable for Clinical Practice January 1972 F. L. MITCHELL, N. VEALL, and R. W. E. WATTS

3 Biochemical Tests for the Assessment of Fetoplacental Function May 1975 C. E. WILDE and R. E. OAKEY

TECHNICAL BULLETINS (price £1·00/$2.00 each)

9 Determination of Urea by AutoAnalyzer November 1966 RUTH M. HASLAM

11 Determination of Serum Albumin by AutoAnalyzer using Bromocresol Green October 1967 B. E. NORTHAM and G. M. WIDDOWSON

13 An Assessment of the Technicon Type II Sampler Unit March 1968 B. C. GRAY and G. K. MCGOWAN

14 Atomic Absorption Spectroscopy: an outline of its principles and a guide to the selection of instruments May 1968 J. B. DAWSON and P. M. G. BROUGHTON

15 A Guide to Automatic Pipettes (2nd edition) June 1968 P. M. G. BROUGHTON

16 A Guide to Automation in Clinical Chemistry May 1969 P. M. G. BROUGHTON

17 Flame Photometers: a comparative list of 17 instruments readily available in Britain August 1969 P. WILDING

19 Spectrophotometers: a comparative list of low-priced instruments readily available in Britain May 1970 C. E. WILDE and P. SEWELL

20 Quantities and Units in Clinical Biochemistry June 1970 P. M. G. BROUGHTON

21 Filter Fluorimeters: A comparative list of 18 instruments September 1970 H. BRAUNSBERG and S. S. BROWN

22 Bilirubin Standards and the Determination of Bilirubin by Manual and Technicon AutoAnalyzer Methods January 1971 BARBARA BILLING, RUTH HASLAM, and N. WALD

23 Interchangeable Cells for Spectrophotometers and Fluorimeters September 1971 S. S. BROWN and A. H. GOWENLOCK

24 Simple Tests to Detect Poisons March 1972 B. W. MEADE *et al.*

25 Blood Gas Analysers May 1972 K. DIXON

26 Kits for Enzyme Activity Determination September 1972 S. B. ROSALKI and D. TARLOW

27 Assessment of Pumps Suitable for Incorporation into Existing Continuous Flow Analytical Systems November 1972 A. FLECK *et al.*

28 Routine Clinical Measurements of Transferrin in Human Serum September 1973 K. DIXON

29 Control Materials for Clinical Biochemistry (5th edition) September 1973 J. F. STEVENS

30 Notes on the Quality of Performance of Serum Cholesterol Assays September 1973 S. S. BROWN

31 Determination of Uric Acid in Blocd and in Urine July 1974 R. W. E. WATTS

32 A Survey of Amino Acid Analysers Readily Available in the United Kingdom September 1974 J. E. CARLYLE and P. PURKISS

33 Definitions of some Words and Terms used in Automated Analysis November 1974 A. FLECK, R. ROBINSON, S. S. BROWN, and J. R. HOBBS

34 Measurement of Albumin in the Sera of Patients January 1975 LINDA SLATER, P. M. CARTER, and J. R. HOBBS

35 Investigation of the Validity of Temperature Correction Factors for Serum Aspartate and Alanine Transaminases March 1975 S. B. ROSALKI *et al.*

36 Factors Influencing the Assay of Creatinine November 1975 J. G. H. COOK