MESONEPHROID (CLEAR CELL) CARCINOMA OF THE OVARY AND ENDOMETRIUM

A Comparative Prospective Clinico-Pathological Study and Review of Literature

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Seventeen cases of mesonephroid (clear cell) primary ovarian adenocarcinoma together with 6 cases of its analogous endometrial tumor have been studied over the decade ending 1976. Eleven of the ovarian tumors and all six of the endometrial tumors formed part of a personal consecutive series of 64 primary ovarian carcinomas and 114 primary endometrial carcinomas seen during the same period, these cases being studied prospectively. The remaining 6 ovarian tumors were studied retrospectively. Aims were to reexamine evidence for considering these tumors as distinct and homogenous groups; to reexamine evidence regarding their histogenesis; to investigate the concordance between the ovarian and endometrial tumor; and to reexamine clinical, pathological, therapeutic, and survival data relevant to these tumors. Full clinical, pathological, therapeutic, and survival details are recorded. It is suggested that present evidence indicates complete compatibility between the three major current views regarding histogenesis of the ovarian tumors; that in only a small proportion of cases is there histogenic coincidence between the ovarian and endometrial lesions; and that, pending further investigation, separation of the endometrial clear cell carcinomas from other nonclear endometrial carcinomas should be on a provisional basis only. Suggestions are made for further investigations into the prognostic aspects of these tumors.

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A REVIEW OF RELEVANT LITERATURE IS COMplicated by the wide variety of names proposed for the ovarian mesonephroid (clear) cell carcinoma, depending largely upon the prime interest of individual author, by the wide range of features considered to be characteristic and necessary for diagnosis, and by the inclusion in many of the earlier reports of tumors now considered to be of a different category.[15,23,35,40,41] However, a degree of simplification can be introduced if articles published prior to 1954 are regarded as belonging to one of two separate but convergent series. The first, beginning with the publication by Schiller in 1939 of a description of ten tumors of the female genital tract considered to arise within mesonephric remnants and characterized by a predominantly tubulo or cystic papillary structure associated with epithelial cells of hobnail type and glomerulus-like bodies.[35] The second, begins with Peham's presentation in 1899 of a tumor of similar structural pattern, but in which the epithelial element was of clear cell or hypernephroid type.[30] The two series merging into a single line in 1954 in the articles by Novak and colleagues[25] and Teilum[42] and recognition of essential identity between the patterns described. Subsequent articles[1,5,16,18,20,26,28,32,44] showed greater homogeneity in the tumors described, a result largely due to recognition of the endodermal sinus tumor (Teilum), a tumor of similar structure, as of germ cell origin with extra embryonic development.[41] Of these later articles that of Kurman and Craig[16] is of interest in that it includes a comparison between primary ovarian endometrioid and mesonephroid tumour types.

Though most modern writers would accept that these ovarian tumors possess clinical and

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pathological features sufficiently distinctive to justify placing them in a separate and distinct category from other ovarian epithelial tumors,[1,7,10,23] controversy still exists regarding their histogenesis and histogenic as well as morphologic identity between the ovarian and endometrial mesonephroid tumor types. Few writers now accept Schiller's extension of Cohnheim's hypothesis that the ovarian tumor arises from mesonephric rests,[35] and support that it either originates in mature Müllerian tissue (endometriotic foci) within the ovary as suggested by Scully and Barlow;[5,10,36] or from pluripotential ovarian surface epithelium, being a variant of endometrioid carcinoma with one sided differentiation;[8] or that it is in effect a variant of mesothelioma arising from pluripotential mesothelium.[32] Of significance in this context are the electron microscopical studies of Okagaki and Richart,[27] and Silverberg,[37] describing both light and ultrastructural findings in single mesonephroid (clear cell) ovarian carcinomas, and the corresponding articles by Silverberg and De Giorgi[38] and Rorat *et al.*[33] describing similar features in the corresponding endometrial tumor.

Acceptance of the endometrial clear cell carcinomas as a distinct and homogenous group, and definition of morphological features necessary for inclusion within such a group is less firmly based. This is due in part to fewer published reports, only two large series of cases having been published, one by Silverberg and De Giorgi[38] and the second by Kurman and Scully;[17] and also partly to the occurence within endometrial carcinomas of nonclear type of focal areas of lipoid degeneration or of secretory change. Thus the presence of clear cells within an endometrial tumor does not warrant a diagnosis of mesonephroid (clear cell) carcinoma.[24] Review of related literature is therefore less complicated and may be based upon the reports of Silverberg and De Giorgi, and Kurman and Scully, these writers giving details of earlier single case reports.[17,38]

MATERIALS AND METHODS

The study began in 1966 and was continued on a prospective basis over the following decade. Eleven of the ovarian tumors were studied prospectively and formed 17% of a personal consecutive series of 64 primary ovarian adenocarcinomas recorded during this period. To these were added a further six cases, relevant data and slides being made available by colleagues. These cases were studied retrospectively. The six endometrial mesonephroid (clear cell) adenocarcinomas were studied prospectively and formed part of a personal series (1.4%) of 144 primary endometrial adenocarcinomas recorded during the same period.

The ovarian tumors were selected on the basis of showing the following microscopic structural patterns either singly or in combination: a) a tubular and cystic pattern in which the predominant epithelial cell was of hobnail or clear type either in pure or admixed form, with or without the presence of intermediate types; b) the presence of simple or complex papillary formations clothed by similar types of cell; and c) the presence of sheets of epithelial cells of clear or granular eosinophilic non clear type, with or without cells of intermediate appearance. An added qualification applied to the tumors studied retrospectively was that similar clinical data should be available, and that an adequate number of histological sections should be available for study. The endometrial tumors were selected on the basis of showing prominent areas of similar structural pattern.

Pathological material was received in an unfixed state, described, recorded photographically, and fixed in 10% formol saline solution for a period of 24 hours. On completion of fixation a minimum of 10 tissue blocks were taken from areas considered representative and haematoxylin and eosin stained sections prepared. If acceptable further sections were stained by Goldner's modification of the Masson trichrome technique; Southgate's modification of Mayor's mucicarmine technique; the periodic acid Schiff reaction both with and without predigestion with diastase; the Sudan IV reaction; and in some cases by the Gomori technique for reticulin. If a total hysterectomy and bilateral salpingo-oophorectomy had been carried out tissue was taken from anterior and posterior cervical lips, endometrium, fallopian tubes, and contralateral ovary and examined microscopically. In the uterine tumor cases a similar microscopic examination of cervix, unaffected endometrium, and adnexa was carried out. Photomicrographs were taken using a Leitz "Ortholux" microscope in conjunction with a Leica 35 mm camera, a green filter and Ilford Pan X film being used for standard haematoxylin and eosin stained sections. Residual wet material was preserved in 10% formol saline solution. Clinical and subsequent data was based upon personal contact with the clinician in charge of the case, upon study of the hospital case notes, and upon contact with the family

practitioner. In all fatal cases the degree of reliability of the stated cause of death was recorded *i.e.* autopsy, limited autopsy, or hospital or practitioner's certificate.

RESULTS

Ovarian Tumor Series

Aetiological, clinical, and therapeutic: The patients ranged in age from 42 to 75 years (mean 52.8 years). All were Caucasians. Nine patients were postmenopausal and the remaining 8 were orthomenstrual. Ten patients were nulliparous (59%); two patients each had one child, and four patients each had two children. In one patient this information was not available. One patient gave a history of two miscarriages as well as two live births. The previous menstrual history of all the patients was within normal limits. Coexistant diabetes mellitus, controlled by insulin and diet, was present in one patient, apart from this no patient was known to be receiving hormone therapy.

Presenting symptoms were those commonly associated with nonhormone producing, intra abdominal, tumor masses. All patients showed a palpable intra abdominal mass to be present on examination, this was associated in 15 (88%) with visible abdominal swelling. Less common symptoms were vaginal discharge (41%); abdominal tenderness (29%); and weight loss (29%). Pyrexia and acute abdominal pain were observed only when associated with torsion or infarction of the ovarian tumor. In two cases the diagnosis was unsuspected on admission, one patient being admitted for investigation of pyrexia, and the other on account of a deep leg vein thrombosis. Nausea and vomiting were present in three cases (18%), and urinary symptoms in one (6%). Clinical signs of a pleural effusion were present in one case (6%). Routine blood examination made at the time of admission showed an iron deficiency anaemia to be present in one case. With the exception of the single diabetic, routine biochemical tests made at the same time, on all the patients were within normal limits. Hormonal studies and calcium and phosphorus studies were not carried out.

Therapy given to these patients varied considerably according to the views of individual clinicians. In 11 (65%) total hysterectomy and bilateral salpingo-oophorectomy were carried out, this being supplemented in six of the patients by anti mitotic chemotherapy and/or irradiation. In six (35%) treatment was confined to the affected ovary with supplementary chemotherapy and/or irradiation in four. Clinical staging (F.I.G.O)[13] showed 9 to be in Stage Ia; 2 in Stage Ib; 2 in Stage Ic; 3 in Stage IIb; and 1 in Stage IV. The tumor was adherent to adjacent structures in 10 (59%), and ruptured at operation in 7 (41%). A hemorrhagic ascites was present in three cases (17.6%). Correlation of postoperative survival with F.I.G.O Stage of the disease is presented in Fig. 1.

Pathology: The tumor was unilateral in 15 patients (88%), in 9 on the right and in 6 on the left. Bilateral tumors of similar morphology were present in the remaining two patients. Maximum tumor diameter ranged from 6 to 23 cm. Externally, the tumors were lobulated and an apparent fibrous capsule was present. Surface excrescences present on some of the tumors suggested capsular penetration. Tumor consistency ranged from soft and cystic to firm and solid. Upon hemisection 13 (76%) showed a macrocystic appearance with irregular, white or grey, glistening solid areas. In the remaining 4 cases the gross appearance was mainly solid with scattered small cysts. Areas of hemorrhage and necrosis were present in all the tumors.

The basic histologic structural pattern observed in all tumors was of tubulo or cystic papillary type, with simple or complex papillary formations extending into tubular or cystic luminae (Figs. 2–5). This pattern was associated with adenofibroma like areas in which small cystic cavities were distributed through a fibrous stroma; areas in which tubular formations predominated; and areas of solid sheets of epithelial cells, of either pure or admixed type, separated by fibro vascular septa (Figs 6, 7). Clefts, cystic structures, glandular, and papillary formations being lined or clothed by one or more layers of epithelial cells of hobnail, clear, or granular eosinophilic type either in pure or admixed form. Transitional epithelial cell forms between granular eosinophilic and clear, and between hobnail and clear were present to a variable degree in all tumors. This was particularly marked in two in which solid epithelial sheets were composed of a narrow zone of granular eosinophilic non clear cells enclosing an area of cells of clear type. Clear and granular eosinophilic cells were present in all tumors, but hobnail type epithelial cells could be demonstrated in only 12 (70%). However, since the 5 tumors in which they were absent were all studied retrospectively this feature may simply be a reflection of limitation of material inherent in such studies. The stromal component of the tumors was fibrotic and ranged from delicate fibrous septa to

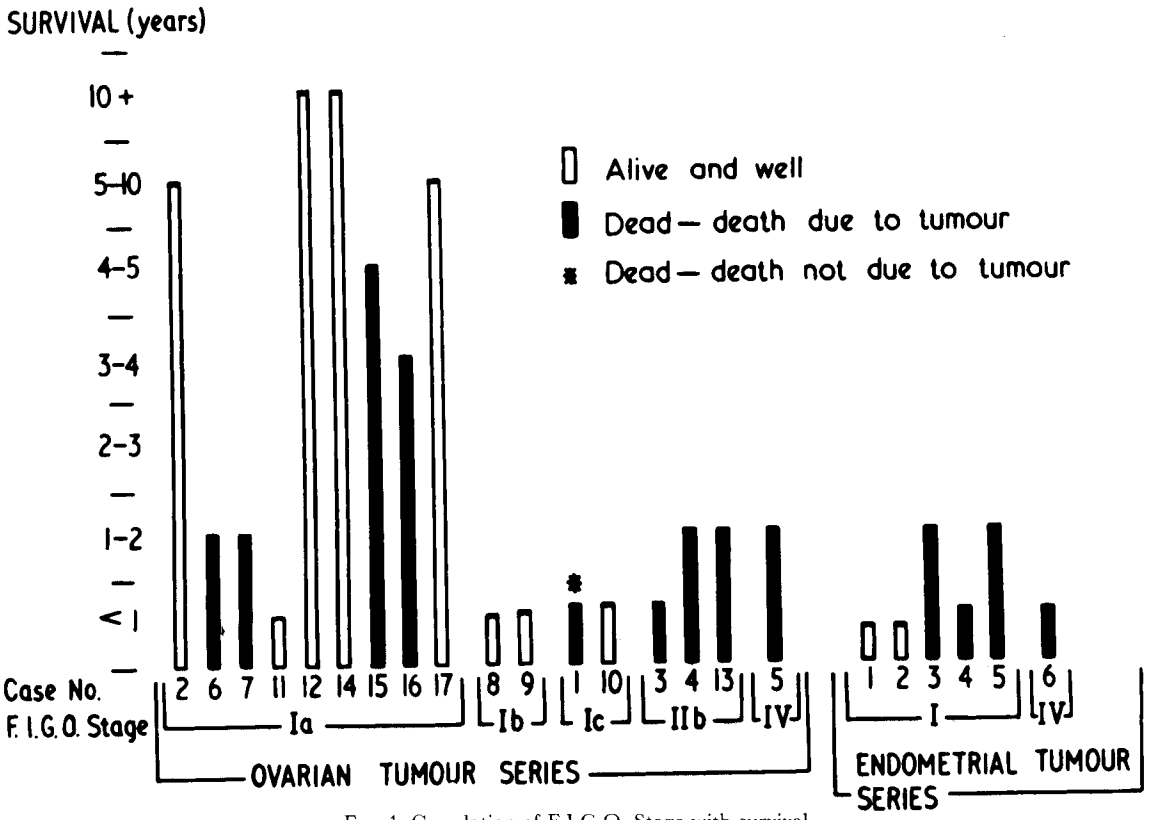

FIG. 1. Correlation of F.I.G.O. Stage with survival.

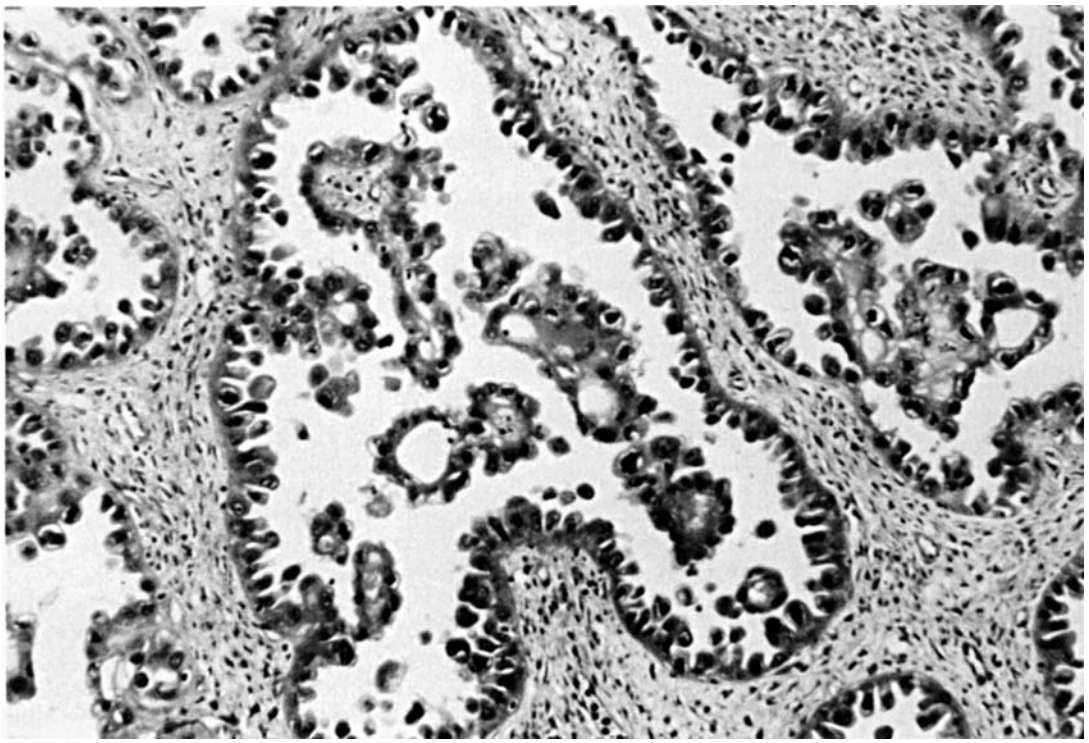

FIG. 2. Ovarian mesonephroid (clear cell) carcinoma: Tubulo-papillary structures showing a predominance of hobnail type epithelial cells (H & E ×100).

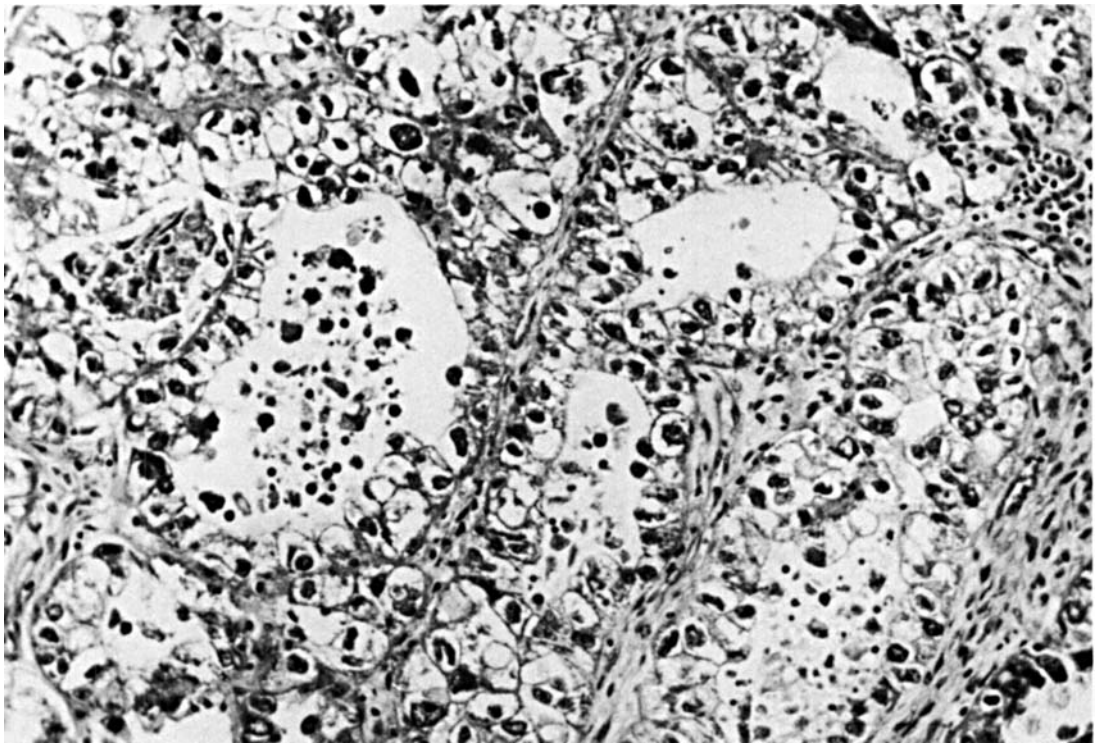

FIG. 3. Ovarian mesonephroid (clear cell) carcinoma: Tubulo-papillary structures showing epithelial cells of predominantly clear type (H&E×250).

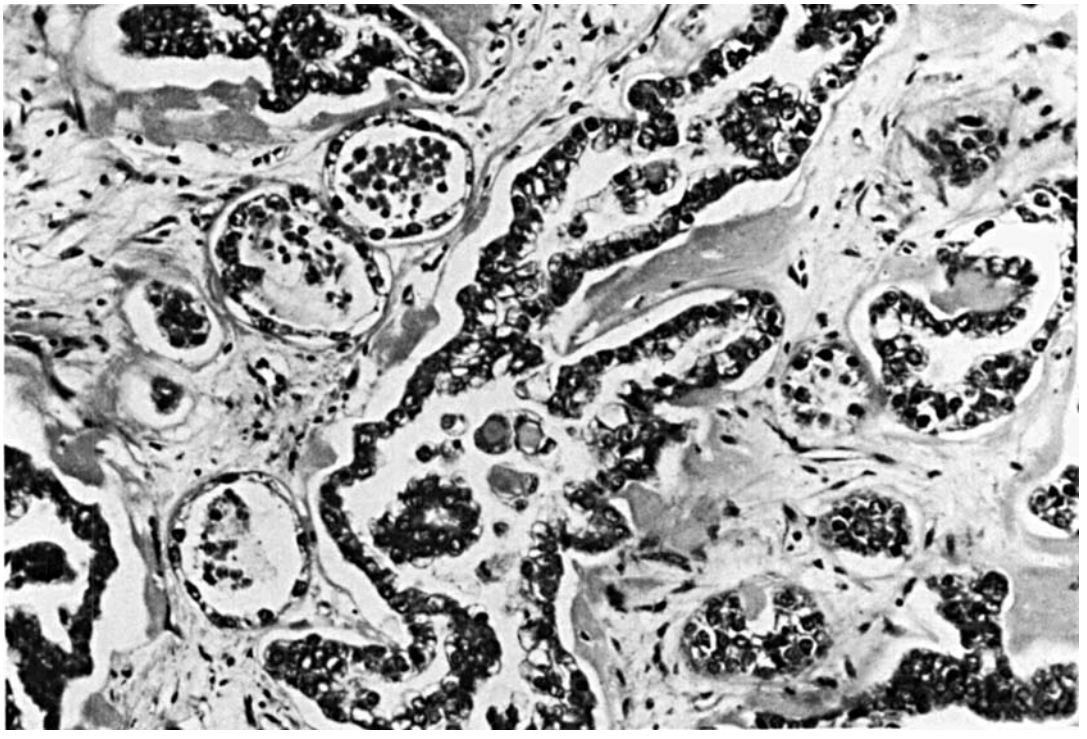

FIG. 4. Ovarian mesonephroid (clear cell) carcinoma: Branched tubular and simple cystic structures with lining epithelium of clear, granular eosinophilic, and transitional types. P.A.S.-positive, diastase resistant material present in stroma and within papillary formations (Diastase-P.A.S.×100).

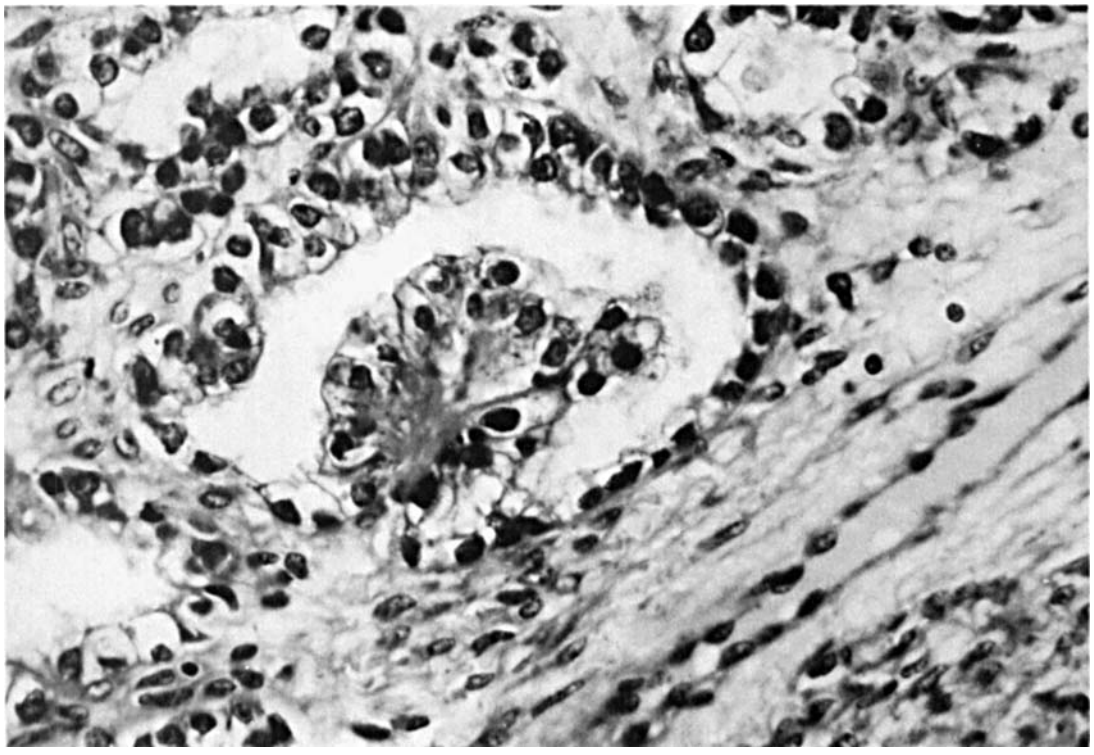

FIG. 5. Ovarian mesonephroid (clear cell) carcinoma: Typical papillary formation extending into cystic cavity (H & E×250).

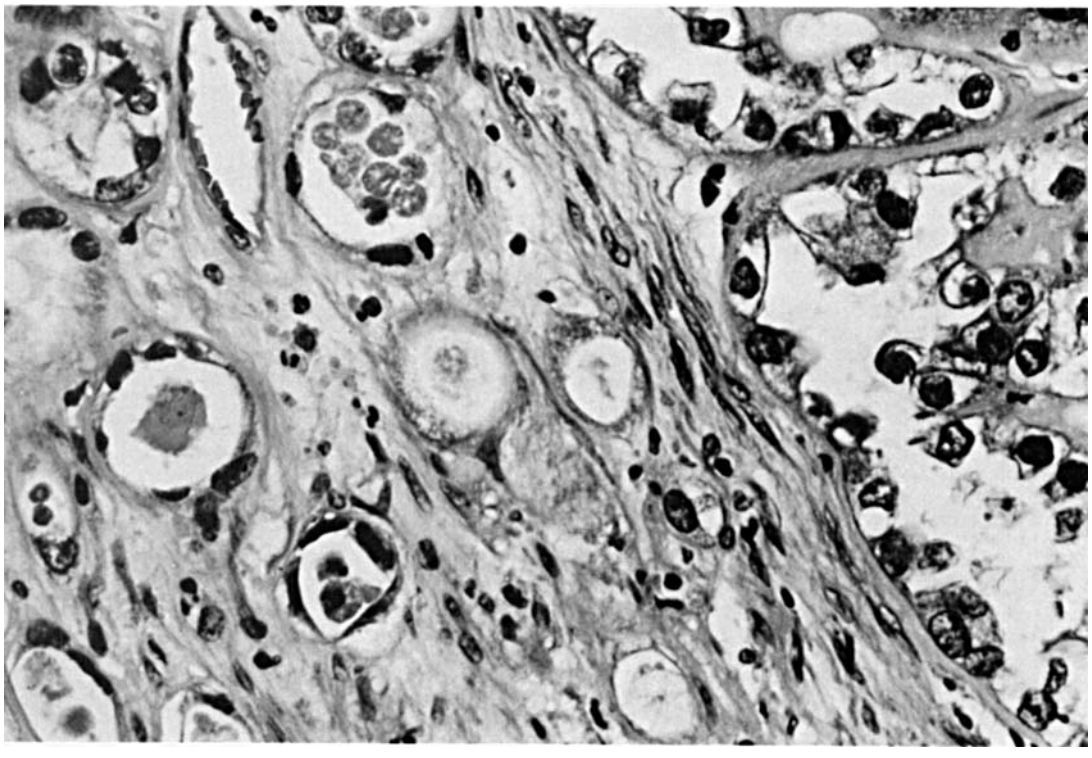

FIG. 6. Ovarian mesonephroid (clear cell) carcinoma: An area showing small and irregular cysts (adenofibroma-like) contiguous with an area of tubular structure and clear cell predominance. (H&E×250).

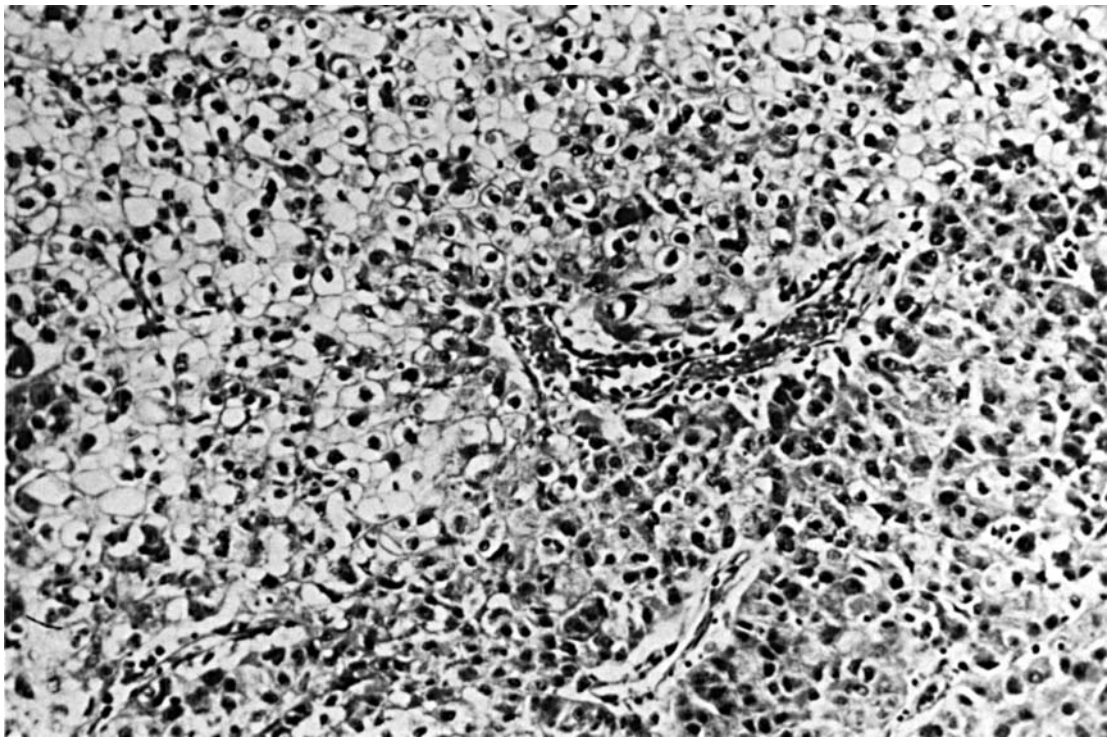

FIG. 7. An area of an ovarian mesonephroid (clear cell) carcinoma showing solid sheets of polygonal cells of clear type contiguous with a similar area in which cells of granular eosinophilic type predominate (H & E×100).

broad bands of relatively dense tissue. Apparent transition of stromal to epithelial cells as recorded by Anderson and Langley[1] was not observed. A striking feature observed in all tumors was the wide variation in relative proportions of the main structural patterns, and of their component epithelial elements, both between different areas of the same tumor and between different tumors of the series.

Epithelial cell and nuclear pleomorphism, though not a prominent feature, was observed in all tumors, being present mainly in areas composed of granular eosinophilic non clear cells or of such cells admixed with clear cells. Such areas showed mitotic figures of both normal and abnormal (tripolar) appearance. Epithelial multilayering and budding were also present to a variable degree in all the tumors, the inter area variability in its intensity being too great to permit quantitative assessment. For the same reason an attempt at assessment of mitotic activity, after the manner of Broders,[3] was abandoned when it became clear that any index obtained could not be considered as representative of the tumor as a whole or even of the most active areas. Calcification was present in 2 (12%) tumors. In one, as rounded or oval intrapapillary bodies showing a curious basophilic speckling (Fig. 8), and in the other as widely scattered small granular foci. Giant cells, when present, were associated with areas of necrosis or degeneration. Two other features of interest were the presence of scattered small islands of polyhedral cells, having a rounded or oval nucleus, and an eosinophilic cytoplasm (Fig. 9), and the presence of strongly P.A.S.-positive diastase resistant cells scattered through a loose fibrous stroma (Fig. 10). Each occurred in a single case.

The response to special staining techniques was similar to that observed in other studies.[1,5,7,22] Mucicarminophilic material was present in cystic and tubular luminae, irrespective of epithelial lining cell type, but not within the cytoplasm of hobnail, clear, or granular eosinophilic cells. P.A.S.-positive material was present in similar situations and also within cells without distinction as to epithelial cell type. Predigestion with diastase showed a variable reduction in response in both cells and luminae, with residual diastase resistant material remaining in both situations. Diastase sensitive P.A.S.-positive material was observed in both particulate and diffuse forms within cells of similar morphology. A wide variation is response was observed in cells

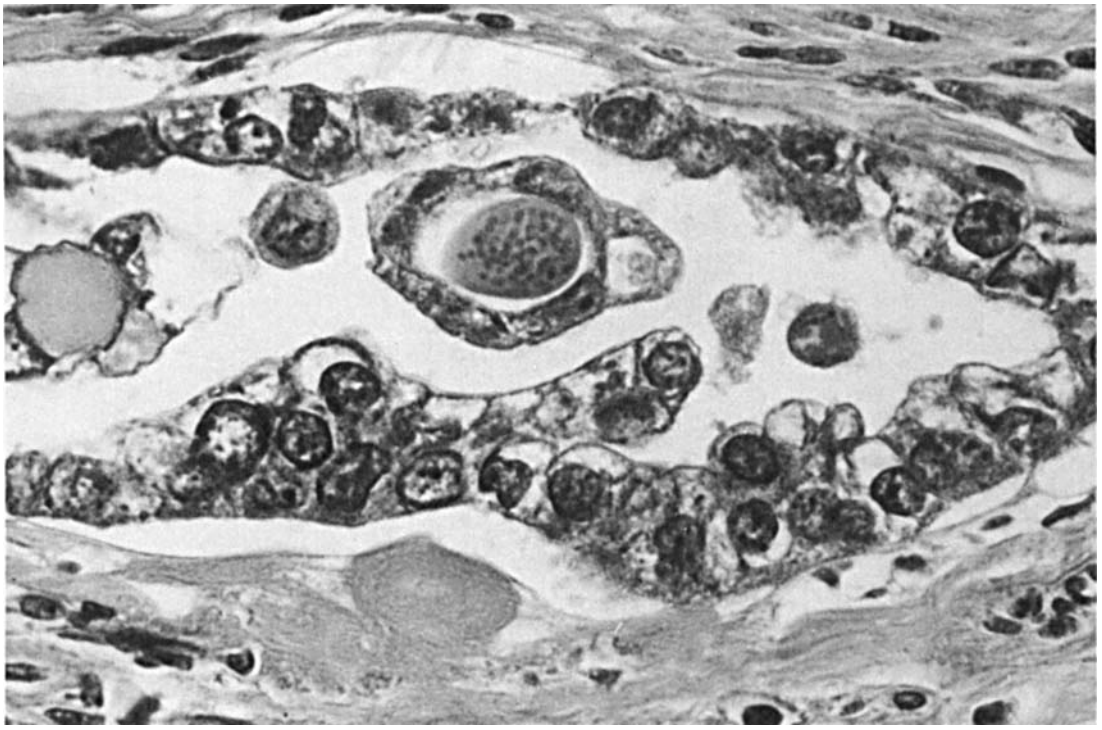

FIG. 8. An intrapapillary, P.A.S.-positive, diastase resistant body, showing speckled calcification. From an area of an ovarian mesonephroid (clear cell) carcinoma in which admixed clear and granular eosinophilic epithelial cells predominated (H&E×400).

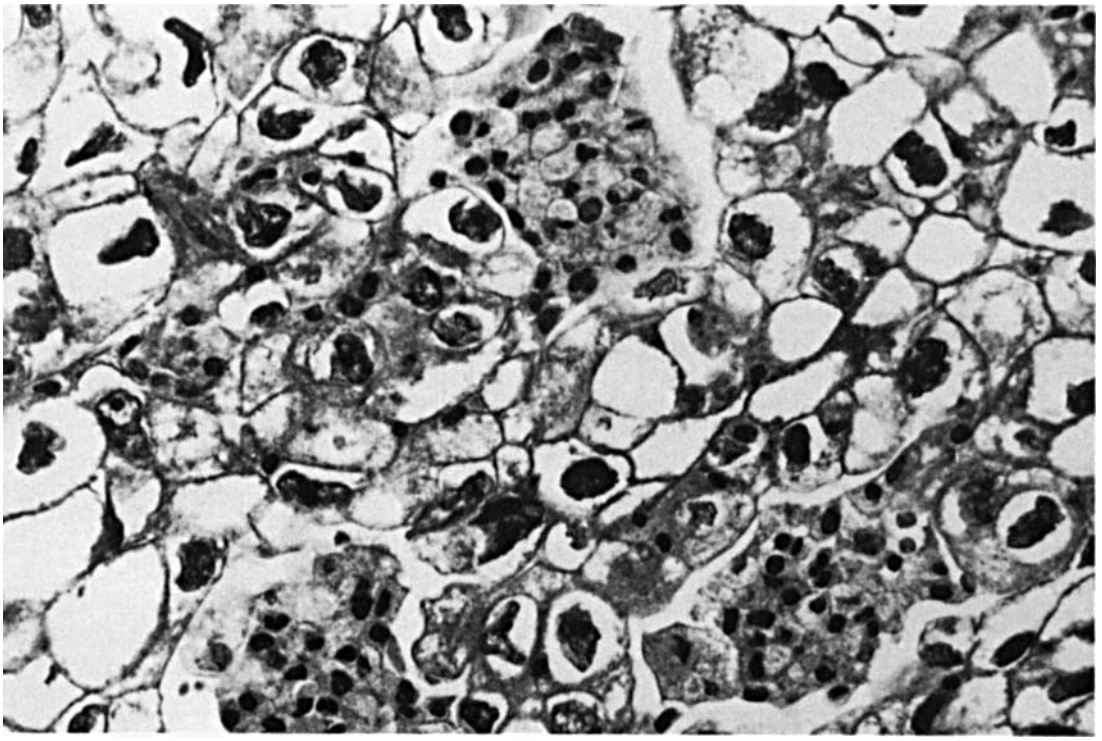

FIG. 9. Ovarian mesonephroid (clear cell) carcinoma: Islands of small, eosinophilic, polyhedral cells from an area in which admixed clear and granular eosinophilic cells predominate, (Masson-trichrome ×250).

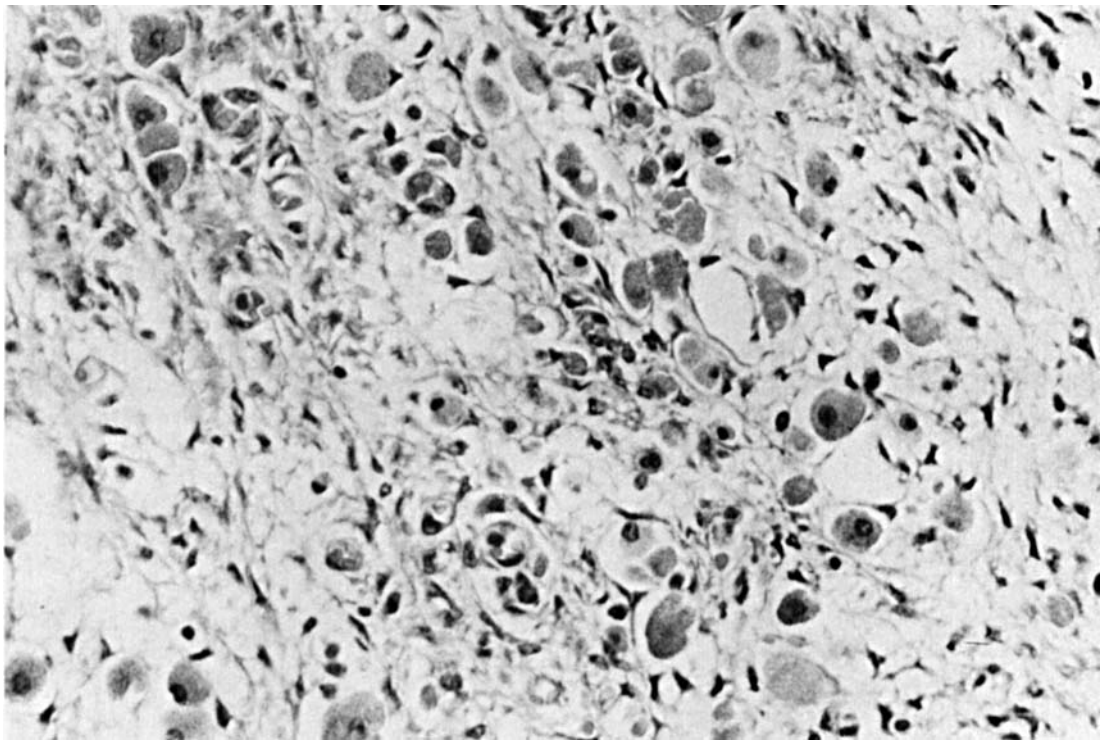

FIG. 10. Ovarian mesonephroid (clear cell) carcinoma: Basophilic, P.A.S.-positive, diastase resistant cells distributed through a fibrous stromal area (H&E ×250).

of similar morphology both within and between tumors. Neutral fat was observed only in association with areas of degeneration or necrosis.

Associated endometriosis was present in 5 (29%) cases. As cysts of the contralateral ovary in three, and within the affected ovary in the remaining two. One of the two cases showed proliferative changes of the lining epithelium, with back to back glandular formations and an appearance suggesting malignant change, however, continuity between this area and the clear cell tumor could not be established. The case notes of another patient recorded endometriosis of the affected ovary as present some ten years previously, the condition being observed during the course of an intra abdominal operation for an unrelated condition. The tumor from this patient failed to show residual evidence of this condition. Unaffected endometrium was available for examination in 15 of the 17 cases (2 patients having had a previous hysterectomy for unrelated disease). In each the specimen showed a microscopic appearance consistent with the stated phase of the menstrual cycle. Other associated lesions were those commonly observed in the female genital tract, multiple fibroids (2 cases); mucinous cystadenoma (1 case); and benign cystic teratoma (1 case).

Endometrial Tumor Series

Aetiological, clinical and therapeutic: The patients ranged in age from 53 to 66 years (mean 60 years). All were Caucasians, and all were postmenopausal. The interval between the onset of the menopause and operation ranged from 3 to 18 years. Three patients were nullipara with no history of abortion; two had two children; and the remaining one, four children. None of the patients was known to have received exogenous hormone therapy, or gave a history suggestive of hormonal imbalance.

The chief complaint of all six patients was one of vaginal bleeding, ranging in duration from 1 to 12 months before admission. This was associated with low back pain (1 case); suprapubic tenderness (1 case); and weight loss (1 case). In three the uterus was enlarged and in the remaining three it was described on clinical examination as normal in size. Three of the six cases showed a moderate degree of hypertension otherwise their general physical examination upon admission was within normal limits for their age group. Routine blood examination carried out on admission showed an iron deficiency anaemia to be present in one case, and a raised blood urea nitrogen level in another. Vaginal cytological examination was carried out on two

patients prior to operation, in one, malignant cells were identified, the second showed inflammatory cells only. In each of the six patients the preoperative diagnosis of carcinoma was confirmed by positive malignant findings on curettage.

In all six patients primary treatment was surgical, *i.e.* total hysterectomy and bilateral salpingo-oophorectomy (5 cases), and total hysterectomy and salpingo-oophorectomy in the remaining one (one ovary having been removed previously for treatment of a benign cystoma). This was supplemented by postoperative irradiation in five, and by postoperative medroxyprogesterone acetate (Provera) therapy in the remaining one. At the time of operation five cases were in F.I.G.O. Stage I of the disease, and the remaining case in Stage IV. Postoperative survival details are presented in Fig. 1.

Pathology: Uterine body size ranged form 8 × 6 × 5 cm to 5 × 5 × 3 cm. With the single exception of the Stage IV case the external appearance of the specimens appeared normal. In two cases the endometrial tumor formed a hemorrhagic and polypoid mass arising in the fundal and upper cavity region and filling the uterine cavity. In the remaining four the major part of the endometrium appeared to be involved in the malignant change. Upon naked eye examination, invasion of the myometrium in the five Stage I cases appeared to extend through less than a fifth of its thickness. That this impression could be grossly misleading was shown when microscopic examination in one of these cases showed more than 75% of the myometrium to be penetrated. No single feature, or combination of features, was observed by which the diagnosis could be made on gross examination.

Microscopic examination showed the predominant structural pattern to be one of irregular clefts, tubular and cystic spaces, or glandular formations lined by one or more layers of malignant epithelial cells. Simple or complex papillary formations commonly extended into the luminae of these structures. Contiguous were areas composed of solid sheets of epithelial cells either in pure or admixed form. In five of the six cases (83%) areas of typical non clear endometrial adenocarcinoma were admixed with those of mesonephroid structure with zones of apparent transition between the two types. As in the ovarian tumors the relative proportions of the different structural patterns, together with those of their component epithelial elements, varied widely both between tumors and areas within the same tumor. In two cases (33%) polyhedral clear epithelial cells, similar to those of the ovarian tumors, showed a marked predominance. In the remaining 4 cases these cells were prominent but not predominant. In all 6 cases areas composed of admixed clear and granular nonclear cells were present together with cells of transitional type. In 2 cases only, were areas present in which the hobnail cell was a prominent feature. Three (50%) of the cases showed areas of secretory epithelial change resembling that of the 17th day endometrium. This appearance was considered by Silverberg and De Giorgi[38] to be part of the characteristic picture of the endometrial clear cell carcinoma, a view not accepted by Kurman and Scully who give cogent reasons for their dissention.[17] Unaffected endometrium in all 6 cases showed regressed, regressing, or active cystic endometrial hyperplasia, a feature suggesting that progesterone, or progesterone like activity, was not a cause of the secretory areas observed in the three cases. Areas of necrosis, inflammatory infiltrate, and hemorrhage were present in all 6 cases. Psammoma bodies as recorded by Kurman and Scully[17] were not present. Mitotic figures were present in all 6 tumors but varied in number from area to area. A representative quantitative assessment of mitotic activity could not be obtained due to this variation. In 1 case (Stage IV) mitotic activity was associated with marked epithelial cell pleomorphism, giant and multinucleate cell forms, and myometrial invasion. Epithelial multilayering was present in all 6 tumors. Small foci of squamous metaplasia were present in 2 cases. Residual unaffected endometrium showed cystic atrophic change (regressed cystic hyperplasia) in 3 cases (50%); regressing cystic hyperplasia, with epithelial multilayering still present, in a further 2 cases; and frank cystic hyperplasia in the remaining one. The associated ovaries, fallopian tubes, and cervix were within normal limits for the age group except in the single Stage IV case of the series. Adenomyosis of the myometrium was present in one of the Stage IV cases.

Histochemical examination by mucicarmine, and the periodic acid Schiff reaction showed a marked variation in intensity of response in different areas of the same tumor, and even between morphologically similar areas. Mucicarminophilic material was present within cystic and glandular luminae but not seen with any certainty within cells. The response was most pronounced in glandular areas associated with granular non clear epithelial cells and least marked in areas of clear cell predominance. In contrast, the glands and cysts of associated cys-

tic endometrial hyperplasia in the unaffected endometrium showed a marked positive reaction within gland and cystic luminae, and a less marked, but well defined, response within the luminal border cytoplasm of the lining epithelium. The periodic acid Schiff reaction followed a similar pattern with P.A.S.-positive material present in clear, non clear, and intermediate epithelial cell types. The effect of predigestion with diastase was difficult to interpret with certainty, but a variable reduction in reaction intensity appeared to have taken place in areas of clear cell predominance. Similar reaction responses were observed in the secretory areas of the 3 tumors showing these changes.

DISCUSSION

Aims of the study were to reexamine evidence relative to the homogeneity of these tumor groups and the justification for separate categoricalizations, to reassess evidence for their histogenesis, and to examine the concordance between the ovarian and endometrial tumor groups, as well as to record all clinical, pathological, therapeutic, and survival data. Most writers now accept that the ovarian mesonephroid (clear cell) carcinomas form a distinct and homogenous group even though its histogenesis remains controversial.

Notable exceptions are Czernobilsky and his colleagues who state categorically that these tumors do not constitute a homogenous entity.[5] They base this view upon their ability to demonstrate different types of clear cell within the tumors, and upon the different proportions of clear to non clear epithelial elements present. Their opinion is based upon purely morphological grounds unsupported by clear cut histochemical differences, and takes no account of the possibility that the hobnail, clear, and granular non clear cell represent different forms of the same basic cell produced by, as yet, undetermined physical or extrinsic hormonal factors as suggested by the numerous transitional forms between these cells recorded in various studies.[5, 28,39] Apart from its distinctive structure and characteristic wide variation in relative proportions of its component patterns, evidence for group homogeneity is also provided by the fact that in two thirds of the cases the tumor is unilateral in contrast to other ovarian tumor groups, and that it is rare under the age of 40 years.[32]

Morphological definition of the endometrial mesonephroid (clear cell) carcinoma and its acceptance as part of a distinct and characteristic group of endometrial adenocarcinoma is more controversial. The common association with, and apparent transitions between, the endometrial non clear cell adenocarcinoma and the clear cell tumor observed in the present study and reported by others,[17,38] supports the view that these tumors may represent a common non clear adenocarcinoma that has undergone metaplastic or degenerative changes leading to the histological picture of the mesonephroid tumor.[24] The work of Kurman and Scully[17] cannot be regarded as absolute proof of group homogeneity, since unlike those of Silverberg and De Giorgi,[38] and the few cases of the present study, their cases were selected upon the basis of an absolute predominance of clear cells and may, in fact, result in sampling bias due to selection from one extreme of a possible structural spectrum. The mean age incidence of 67.8 years (S.D. 16.5) of Kurman and Scully's cases, or of 64 years (S.D. 9.9) of Silverberg and De Giorgi's[17,38] contrasts with the mean of 57 years for endometrial adenocarcinoma in Willis' series, and for the means of 53 years, 54 years, and 56 years in three other case series cited by him,[45] and though this difference is suggestive further cases of endometrial clear cell carcinoma need to be examined for its statistical significance to be assessed; nor is convincing evidence of group homogeneity, separate from the non clear adenocarcinomas, provided by clinical or histochemical differences between the two tumors. More convincing is the demonstration by electron microscopy of stacked rows of granular endoplasmic reticulum and massive glycogen accumulations within the cells of the endometrial clear cell carcinoma, features not observed in other endometrial tumors.[33,38] However, this finding is as yet based upon a few single cases and requires further confirmation to assess its full significance. Neither clinical profile or histogenesis provide evidence warranting the endometrial clear cell carcinoma to be considered distinct and separate from other common endometrial carcinomas. It is therefore suggested that group status for these tumors should be considered at best as provisional, pending further investigation and an acceptable morphological definition with stated limits of permissible variation.

Morphological identity between the ovarian tumor and its analogous endometrial tumor has been proposed by many writers[27,33,37,38] and claimed as providing strong support for a common histogenesis. Structural similarities have been described at ultramicroscopical as well as

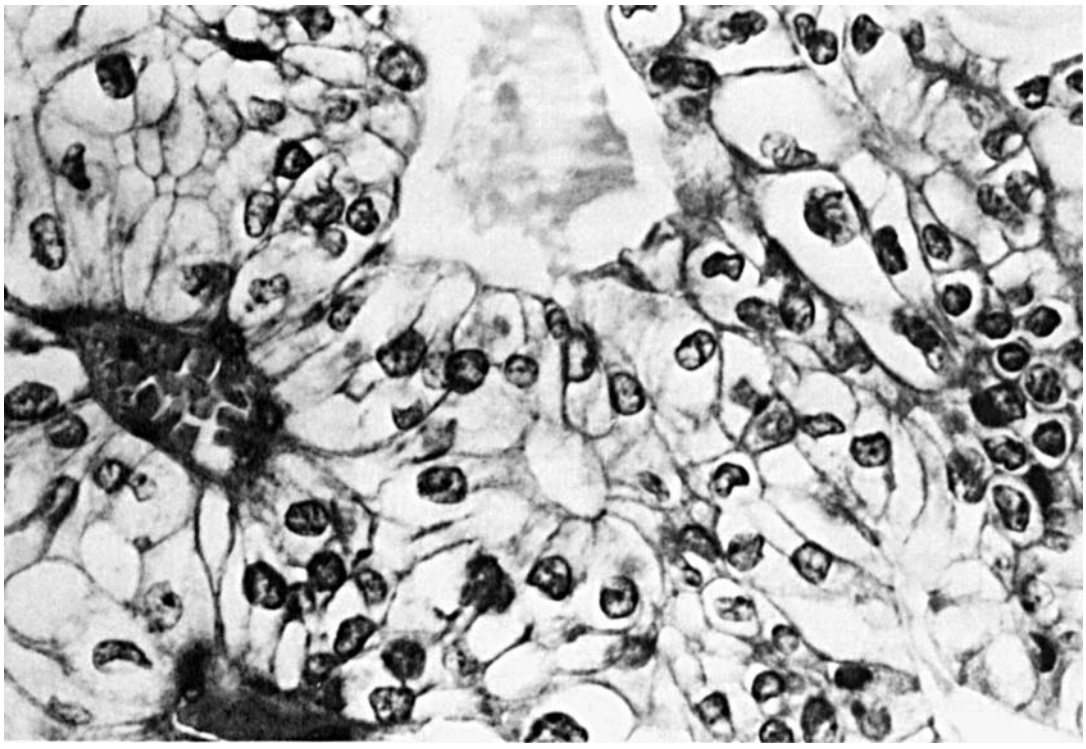

FIG. 11. Endometrial clear cell carcinoma: Tubular pattern with tubules lined by clear cells (Case 2, H&E ×400).

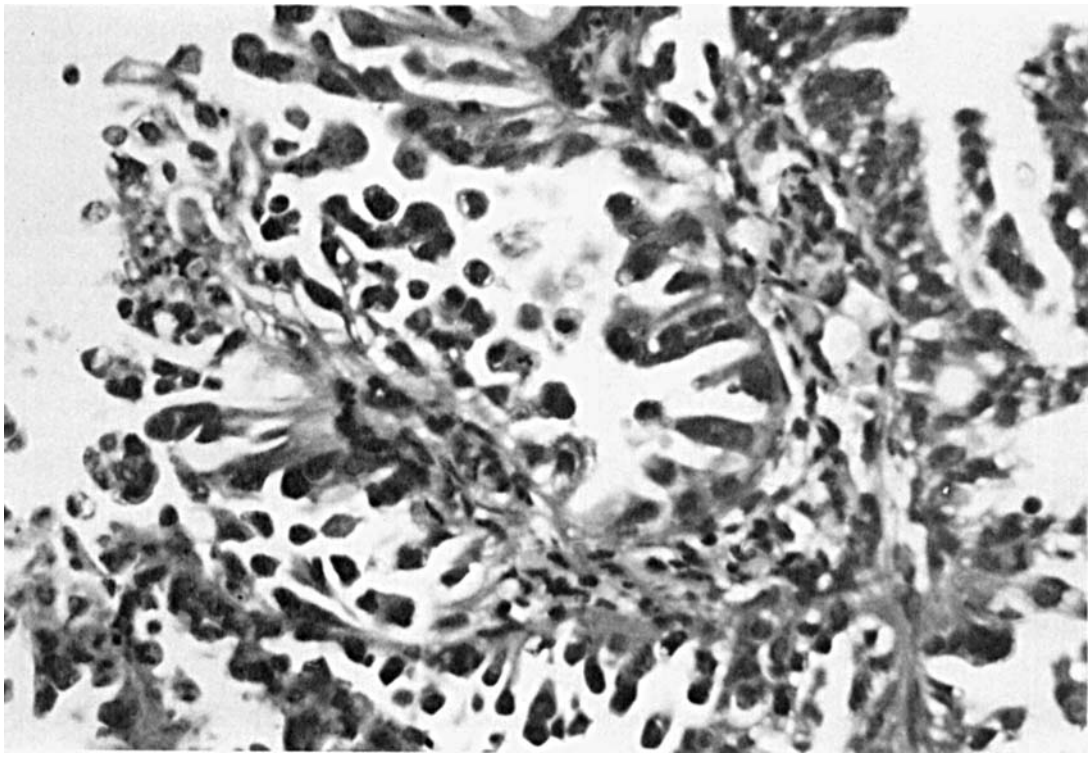

FIG. 12. Endometrial clear cell carcinoma: Papillary area with marked predominance of hobnail epithelial cells and occasional clear cells (Case 2, H&E ×250).

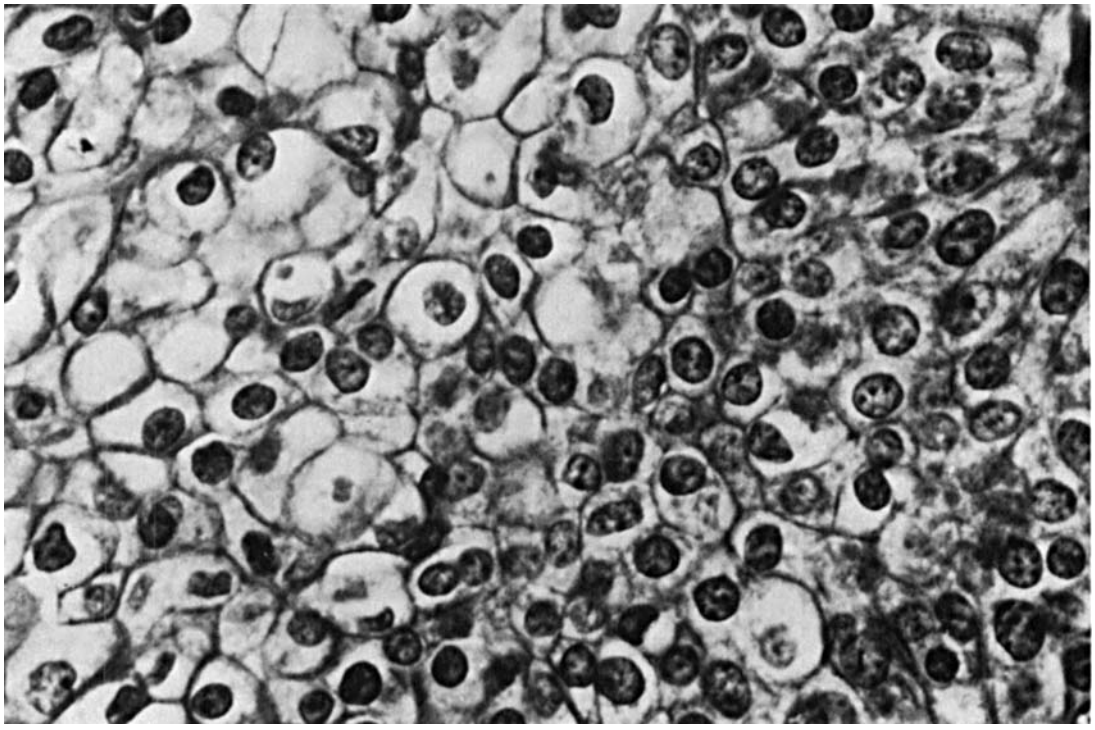

FIG. 13. Endometrial clear cell carcinoma: Transitional zone between area composed of solid sheets of clear cells and similar area with sheets of granular eosinophilic cells and intermediate types (Case 2, H & E ×400).

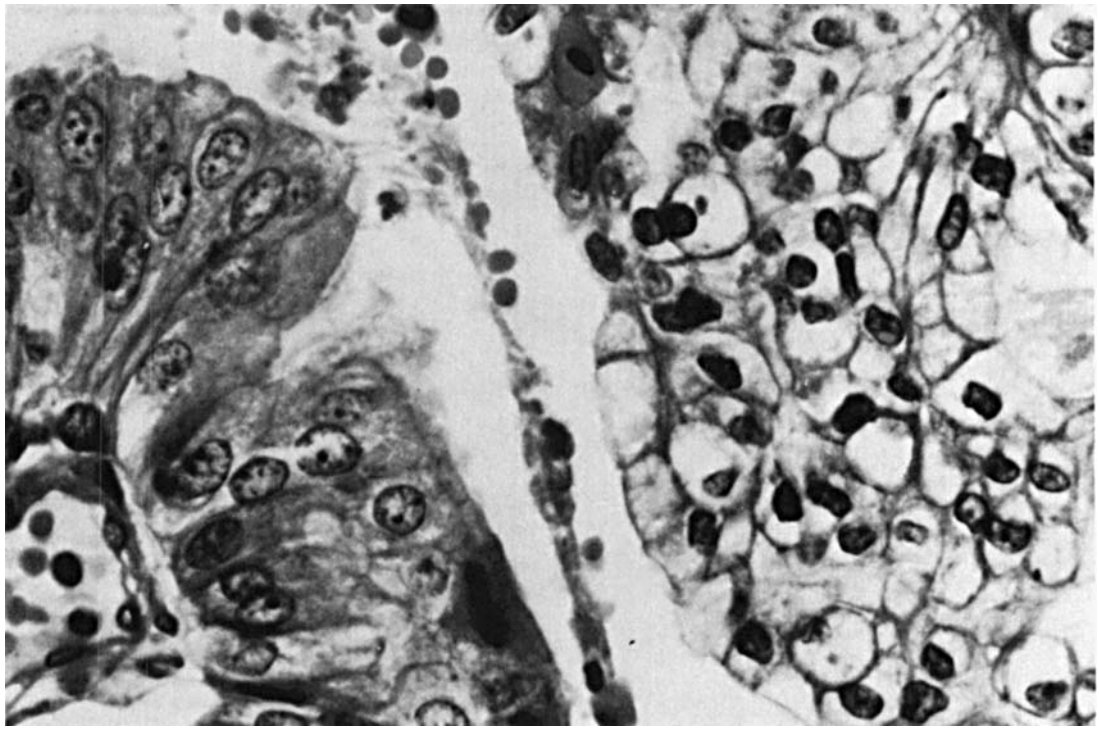

FIG. 14. Endometrial clear cell carcinoma: Area composed of solid sheets of clear cells contiguous with a cystic-papillary area showing multilayering of cells of common nonclear endometrial carcinoma type (Case 2, H&E ×400).

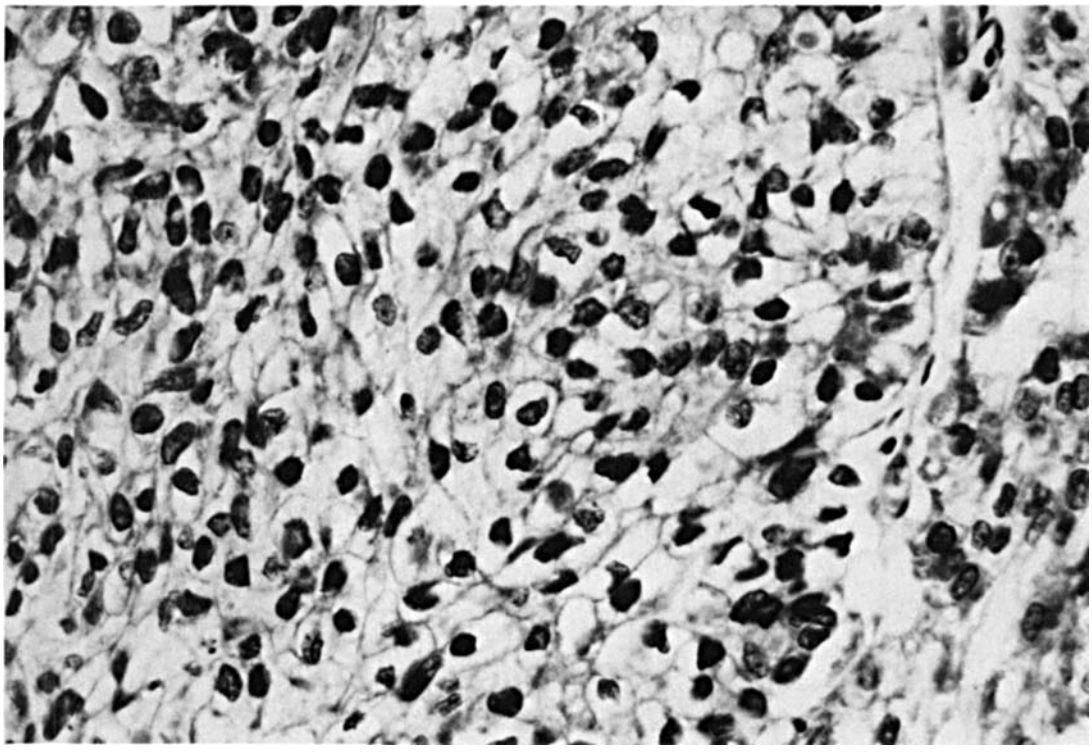

FIG. 15. An area composed of solid sheets of clear cells from and endometrial clear cell carcinoma (Case 6, H&E ×250).

light microscopical levels.[37,38] Certainly at the former level areas can be found in tumors from both sites from which it would be impossible to state in which site the tumor was arising. An observation confirmed by published photomicrographs and by experience in the present study. However, two major morphological differences which exist between the ovarian and endometrial lesions require explanation. First, the existence of so called secretory epithelium in some endometrial tumors, and their absence, so far as the writer is aware, in the ovarian tumors; and second, the frequent admixture of areas of typical nonclear adenocarcinoma with clear cell carcinomatous areas in the endometrial tumor.[17,38] A possible explanation of the first may be that only a small proportion of the ovarian tumors originate from mature Müllerian epithelium, while the majority originate in tissue of coelomic derivation that has lost its capacity for differentiation in this direction, and with it the possibility of this response. The second, while possibly the result of a common carcinogen acting to produce two co-existent tumors of different histogenesis, appears—by reason of the transitions commonly recorded between the endometrial nonclear cell and clear cell carcinomas[17,38]—more probably to reflect the overwhelming importance of mature Müllerian tissue in the production of endometrial adenocarcinomas as opposed to those of the ovary. Further support for the morphological, but not necessarily complete histogenic identity, between the ovarian and endometrial tumor groups is provided by the electron microscopical studies of Silverberg,[37] Silverberg and De Giorgi,[38] and Rorat and his colleagues,[33] work indicating striking similarities in structure between the endometrial and ovarian mesonephroid (clear cell) carcinomas.

Few would challenge the prime importance of endometrium (mature Müllerian epithelium) in the histogenesis of both the nonclear and clear cell endometrial adenocarcinoma, its importance in the histogenesis of the ovarian mesonephroid (clear cell) carcinoma is more controversial. The theory postulating an origin from endometriotic epithelium was first suggested by Scully and Barlow in 1960[36] and since this time has received considerable support.[5,10,36] It is based upon the frequent association of endometriosis with the tumor;[7,16,22,26,31,36] upon transitions observed between endometriotic and clear cell tumor epithelium;[42] upon the association of

the tumor with endometriotic ovarian cysts;[31,36] and upon the electron microscopical studies of Silverberg.[37] It is further supported by similarities observed, in both light and electron microscopical studies, between the ovarian tumor and tumors of similar morphology, occurring at extra ovarian sites in the female genital tract, at which a Müllerian origin appears most likely.[26, 33,36,37] Such a view does not explain the great majority of cases in which ovarian endometriosis cannot be demonstrated, even if allowance is made for the fact that a small focus of endometriosis could well have been obliterated by the tumor. To explain this discrepancy, a second theory of origin suggested pluripotential ovarian surface epithelium of the ovary is the primary source of the tumor and relegated endometriotic foci to a secondary role.[7,16,22] These writers while not excluding ovarian endometriosis as a source of the ovarian tumor relegate it to a secondary role. As Fine and his colleagues observe, displacement of endometrial tissue is an unnecessary postulate in view of the pluripotential of the ovarian surface epithelium.[7] Against such an origin is the high proportion of unilateral tumors observed by Rogers and colleagues, a distribution contrary to the usual findings in ovarian cancer of germinal epithelial origin.[32]

The third view, indicating an origin from pluripotential mesothelium, was suggested by Rogers and colleagues in 1972. These investigators considered that the accumulated data from a study of 95 cases of ovarian mesonephroid carcinoma did not justify acceptance of a paramesonephric (Müllerian) origin. In their view a mesothelial origin was justified by the histological patterns observed and would also account for the occasional concurrent presence of paramesonephric elements.[32] That the tumor is a mesothelioma receives further support from comparison of observed histological patterns and those of malignant mesothelioma as described by Enzinger and colleagues;[6,8] from malignant transformation of epithelium at the ovarian-Fallopian tube junction observed in three of Fine and colleagues cases;[7] and from the electron microscopical studies of Okagaki and Richart suggesting similarities between the cells of the ovarian tumor and those of mesothelium.[27] Against this must be set the observations of Silverberg and De Giorgi who recorded quite different ultrastructural features between the ando-

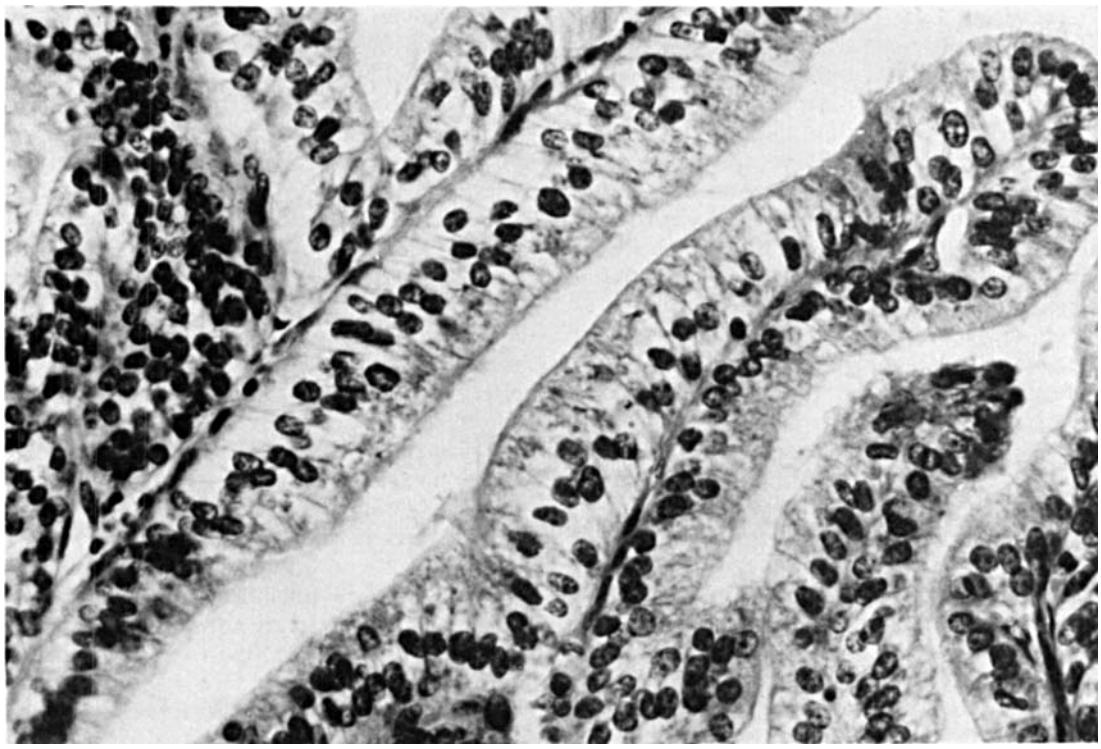

FIG. 16. An area from the same case as Fig. 15 showing a tubulo-papillary structural pattern with epithelial component of typical secretory type (H&E ×250).

metrial clear cell carcinoma and pleural mesotheliomas and Brenner tumors, but similar features between the ovarian and endometrial tumors.[37,38] However, this latter finding, while supporting a Müllerian origin in the single ovarian and endometrial tumors examined by these writers, does not exclude the possibility that another is of greater importance in histogenesis of the ovarian lesion. Fox and Langley discuss the question in some detail and consider that evidence of a mesothelial origin for the ovarian mesonephroic carcinoma to be suggestive but not conclusive. These authors also give an interesting discussion of Farmley and Woodruff's examination of the thesis that all common epithelial tumors of the ovary form a single group arising by mesothelial transformation.[9,29] These three views are not irreconcilable, the evidence of published studies suggesting that the ovarian tumor, unlike its analogous endometrial tumor in which one tissue of origin predominates, can arise from more than one potential source. What is difficult to determine without further extension of electron microscopical studies, and possibly immunohistological techniques relative to hormonal binding, is the relative importance of such potential tissues of origin. In all three theories the suggested tissue of origin derives from coelomic epithelium. In the first two a potential for Müllerian differentiation is developed in one, and latent until stimulated in the other, while in the third the tissue of origin appears to have progressed sufficiently far along the developmental cell line that it has lost capacity for such differentiation, tumors derived from this source thereby showing features common with other mesotheliomas. Also of importance in this context is Needham's hypothesis that certain tissue components in the adult ovary retain competence to develop along lines available to the tissue of origin (Anlage) in embryonic life.[21]

Of clinical and pathological features claimed to correlate positively with outcome, that of tumor spread as observed at operation (F.I.G.O Stage) has been shown to be of great significance in both the endometrial and ovarian tumors.[5,7,16,17,18,20,25,28] This finding is supported by the present study in regard to the ovarian tumors. Other factors claimed to indicate a worsening prognosis in the ovarian tumor group include the presence of a malignant ascites; the presence of bilateral tumors of similar morphology;[5,28] a large tumor size;[22] and tumor rupture at operation.[16,20] Clinical features for which an association with outcome has not been demonstrated in either the ovarian or the endometrial tumor groups include ethnic group, parity, and menstrual phase. Of microscopic features claimed to correlate positively with outcome, most prominent are attempts to grade mitotic activity after the manner of Broders. The claim being made that a high mitotic index indicates a worsening prognosis,[18,27] this claim could not be substantiated by other workers.[1,32] Kurman and Scully attempted a similar grading in their endometrial clear cell carcinoma series but were unable to demonstrate a correlation with outcome.[17] The wide variation in mitotic activity observed between different areas of the same tumor in the present study leads to the view that such results cannot be considered representative of the tumor as a whole, or even of the most active areas, unless multiple sections from many areas are available for study, a situation only likely to occur in a prospective study. An index less liable to sampling error would appear to be that of epithelial to total cell ratio, shown to correlate positively with outcome by Anderson and Langley in their ovarian tumor series.[1] Other microscopic features investigated in relation to the ovarian tumor, but not appearing to correlate significantly with prognosis include; a predominance of either hobnail or clear cells; the ratio of clear to nonclear epithelial elements; cell and nuclear atypia; pleomorphism; epithelial multilayering and budding; necrosis; calcific deposits within the tumor; and stromal proliferation.[1,5,22,32] The significance of these latter factors has not yet been determined relative to the endometrial clear cell carcinoma, but Silverberg and De Giorgi record that they were unable to correlate definitely any one histological pattern with either a better or a worse prognosis.[38]

In common with nonclear endometrial adenocarcinomas, depth of myometrial invasion has been claimed to be of value in assessing prognosis in the endometrial clear cell carcinoma case.[17] Invasion of less than 0.5 cm indicating a better outcome than one greater than this. It has long been recognized that actual invasion as shown by microscopy may be very much greater than apparent invasion to naked eye examination. This was very apparent in one case of the present series in which an apparent invasion of less than 0.5 cm was seen on microscopy to involve almost the full thickness of the myometrium. It is difficult to see how any measurement of invasion, not based upon examination and measurement in multiple sections from multiple planes radial to the axis of the uterine cavity—a situation rarely met with in a retrospective study, can be considered representative of the tumor as a whole or indicative of the maximum degree of invasion.

Reported postoperative survival for the ovarian mesonephroid (clear cell) carcinoma has varied from 15 to 53% for the 5-year period.[5,7,16,18,20,25,28,32] This is due in part to lack of homogeneity in some of the earlier series but also in part to difference in the method of calculating survival statistics. In such circumstances comparisons between the different case series are difficult and in many cases impossible. Survival figures for the endometrial clear cell carcinoma are, at the present time, based upon the reports of Silverberg and De Giorgi (12 cases)[38] and Kurman and Scully (21 cases),[17] the former recording an actuarial rate of 20.6% at 5 years, and the latter a rate of 55.3% after the same time interval. Both these investigators observe that these figures are somewhat lower than those recorded for endometrial adenocarcinoma in general, and the suggestion is made that this adenocarcinoma should be considered one of the less favourable types of endometrial cancer.[38]

The high malignant potential shown by both the ovarian and endometrial tumor makes assessment of prognosis of particular importance in indicating to the surgeon the need for a particular line of adjunctive therapy, as well as give guidance in the social handling of the patient. An opinion as to probable outcome may be subjective and based upon the accumulated experience of the assessor, or it may be objective with attempted mensuration of relevant factors. In the tumors studied previously, attempts at objective assessment have been based upon the relationship of single factors to outcome, examples been the correlation of mitotic activity (Broders Grade), or of tumor spread (F.I.G.O Stage) with outcome. A refinement of this technique that has not, so far as the investigator is aware, been applied to the ovarian tumor is that of discriminant function analysis. In this technique a single prognostic index is obtained by the combination of assessments from multiple clinical and pathological factors, each factor being weighted according to its degree of significance as shown by its correlation with the 5-year and 10-year survival rates and the disease specific death rates. An approach of this type is illustrated by Cochran's work on prognosis in malignant melanoma,[4] work confirmed by the author and colleagues as well as by other workers.[2,19] It would appear eminently applicable to both the ovarian and endometrial lesions but would only be feasible if carried out with the number of cases available at a major tumor registry.

A first step in the diagnosis of the ovarian mesonephroid (clear cell) carcinoma is to exclude the possibility that an ovarian lesion is a metastasis from a tumor of similar type arising at an extra ovarian site within the female genital tract. A second step is to exclude the possibility that the lesion is a metastasis from an extra genital carcinoma of similar structure *e.g.* the renal hypernephroma. In the present series the main difficulties of diagnosis arose in differentiating the ovarian tumor from papillary serous cystadenomas, or carcinomas, showing papillary formations and occasional areas of hobnail change, and from ovarian endometrioid carcinomas showing foci of clear cell change. The former may be differentiated by the fact that tubules, small cysts, and clear cells are rarely encountered, the latter by the fact that it is rare for endometrioid carcinoma of the ovary to show hobnail type epithelial cells or the degree of structural variation observed in the mesonephroid (clear cell) carcinoma.[9] Other ovarian tumors which may cause confusion include adenomatoid tumors, lipoid cell tumors, and the endodermal sinus tumor (Teilum). This last tumor did not occur in the 64 primary ovarian adenocarcinomas observed during the decade of study. That it may closely resemble the mesonephroid carcinoma is shown by its inclusion in many of the earlier reported case series. The tumor, defined by Teilum as "a highly malignant germ cell tumor showing as essential elements a selective (unilateral) overgrowth of extra embryonic mesoblast associated with yolk sac endoderm lining characteristic sinusoid spaces or endodermal small cystic cavities or (vitelline) vesicles,"[43] has been recorded at both gonadal and extra gonadal sites.[11,12,34] Unlike the mesonephroid carcinoma it occurs predominantly in children and young adults. The characteristic structural feature being the presence of mantled perivascular formations consisting of a central capillary with a surface layer of cuboidal epithelium, the whole being enclosed within a capsular sinusoid lined by flattened epithelium. Further features of distinction from the mesonephroid tumor are the absence of clear cells[9] and the presence of alpha-foetoprotein in the patient's serum.[34]

Within the endometrial clear cell carcinoma series, the principle difficulties of diagnosis arose from nonclear cell endometrial carcinomas showing foci of lipoid degeneration or of secretory change. When such foci formed only a very small part of the structural pattern the tumor was classified without difficulty as a nonclear cell adenocarcinoma. It became especially difficult in those cases showing a prominence but not a predominance of clear cells of nonsecretory

type. In such cases, in the absence of a firm acceptable morphological definition of the tumor based upon many more cases than those already published, diagnosis tends to be subjective and to depend upon what the individual worker believes to be the minimum clear cell content upon which the diagnosis of clear cell carcinoma can be made. A difficulty increased by the tendency for nonclear endometrial adenocarcinomas to show a tubular pattern lined by flattened cuboidal peg-like cells indentical to the described in the Schiller mesonephroma.[24]

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