STROMAL ENDOMETRIOSIS*

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Stromal endometriosis, first described by Casler[1] in 1920, is a rare uterine neoplasm characterized by overgrowth of stromal endometrial cells accompanied by endometrial gland structures and always mistaken clinically for fibroids.

In the majority of instances the disease is essentially benign in its orderly cell and mitotic pattern, non-infiltration of muscle and connective tissue and clinical behaviour. It is, however, potentially malignant, or frankly so, because of the tendency to recur locally and even rarely in distant organs such as bowel, lung and brain at unpredictable intervals of time. It can cause death. A minority of women with this lesion manifest frankly sarcomatous variations histologically and clinically, in that extensions after operation are less circumscribed, infiltrating normal tissue and exhibiting lack of cellular and mitotic uniformity so characteristic of its benign counterpart.

This paper presents for the first time in South African literature 2 cases of stromal endometriosis, with a short outline of the pathological and clinical features of the disease.

CASE REPORTS

Case 1

A woman aged 32 years, gravida 2, para 2, had been married for 7 years. She was seen for the first time on 15 December 1952. Her main complaints concerned prolonged and excessive menstrual periods with pain for the last 8 months.

On examination there was no evidence of clinical anaemia. An enlarged uterus the size of a 16-weeks gestation was noted, studded by multiple fibroids but not tender. The cervix and ovaries were normal.

Multiple myomectomy was performed on 20 December 1952 and several subserous and 2 larger submucous fibroids were easily shelled out after bisection of the uterus (unfortunately histological examination was not performed). The ovaries and tubes were normal and were left *in situ*.

On 8 February 1954 the patient had complained of lower abdominal pain and menorrhagia. The uterus was enlarged and tender and fixed to the anterior abdominal wall. Fibroids were not felt. Intramuscular testosterone was prescribed and this controlled the menstrual loss. The pain, however, persisted although it was less severe.

On 25 May 1955 she reported that she had passed a large clot *per vaginam*. Examination of the clot revealed a perfectly formed endometrial cast, which histologically revealed blood clot and stromal cells with no evidence of endometritis.

On 15 August an endometrial cast was again passed. The cervix was found to have a patulous internal os admitting a finger. On 30 September a diagnostic dilatation and curettage was performed. Curettings were histologically normal. The uterus was now the size of a 16-weeks pregnancy, with a markedly enlarged cavity which, on intra-uterine digital examination, showed no recurrence of fibroids. A fixed, solid mass was felt in the left fornix, extending to the left lateral pelvic wall, and it was fixed anteriorly to the bladder base.

Laparotomy was performed on 20 November. A symmetrically enlarged uterus was found, fixed to the anterior abdominal wall. Fibroids were not seen. A fixed solid tumour mass was felt and seen extending into the broad ligament to the left wall of the pelvis and to the base of the bladder. The left ureter was dilated proximal to the invading growth which encircled it for a distance of about 3 inches and was easily shelled out. Total hysterectomy with bilateral salpingo-oophorectomy was performed. No attempt was made to excise the invading neoplasm because of its extensive and intimate attachments.

Histology report (Prof. C. J. Uys) (Figs. 1 and 2). The fundus contained a soft polypoid mass which extended into the myometrium and parametrium on the left side. Histology showed features of an infiltrating sarcoma. Mitotic figures were scanty, and pleomorphism was not striking but there was evidence of tumour embolism into the myometrial vessels. The features of the tumour were consistent with origin from a fibromyoma.

Fig. 1. Low-power magnification of a section of the tumour of case 1.

Fig. 2. High-power magnification of the same section as in Fig. 1.

*Date received: 16 June 1969.

The patient was referred for radiotherapy, but the nature of the neoplasm was considered to be unsuitable for treatment.

On 19 March 1956 the patient complained of frank haematuria. Pelvic examination revealed a solid fixed mass filling the pelvis. Cystoscopic investigation showed bullous formation at the base of the bladder. As a last resort a full course of X-ray therapy was administered. Within 8 months urinary symptoms had completely subsided, as had the pelvic mass. Examination on 13 December proved the patient to be completely well and there was only slight induration of the pelvic structures. Up to 16 March 1968 she has remained completely well.

Reassessment of tumour histology was done on 17 March 1961 by Prof. C. J. Uys and the histology was found to be that of stromal endometriosis.

Case 2

A woman aged 46 years, gravida 5, para 5, was seen on 17 July 1968. Her main complaints were menometrorrhagia and continuous lower abdominal pain for 6 months. In 1958 she had had a resection of a right cystic ovary and an appendicectomy. In 1965 a brain tumour had been removed. It had proved to be a frontal meningioma.

Her menstrual periods had been prolonged in the past 6 months, lasting 10 - 12 days with the passing of large clots and accompanying lower abdominal pain of a continuous nature. Frequency of micturition and stress incontinence were also noted.

Clinically the patient was not anaemic and a blood investigation revealed no abnormalities. A midline lower abdominal swelling was seen and felt extending from the pelvis; irregular in outline, this mass was tender and the size of a 4-months gestation. Marked genital prolapse was noted, with a hypertrophied, non-patulous cervix. The size of the uterus corresponded with the abdominal mass, and it was found to be markedly adherent to the anterior abdominal wall. The ovaries were not felt. A Papanicolaou smear showed no malignancy.

An enlarged uterus due to fibroids was suspected, in addition to marked genital prolapse, and on 29 August 1968 a Manchester operation was performed with high amputation of the cervix. Hysterectomy via the vaginal route was not considered, because of the marked adhesion of the uterus and the size of the organ. A preliminary curettage revealed normal material histologically. An abdominal subtotal hysterectomy was next performed after extensive adhesiolysis, which included small and large bowel. The ovaries were also removed and appeared to be normal. Convalescence was uneventful.

Pathology report (Dr H. Rifkin) (Figs. 3 and 4). A circumscribed tumour mass which was 7 cm. in diameter and yellowish-white in colour was present in the uterine wall in its anterior aspect.

The tumour showed masses of endometrial stromal cells in between muscle bundles. These masses of cells had well-circumscribed margins and contained numbers of thick-walled blood-vessels. The stromal cells were regular and contained about 3 mitotic figures per 10 high-power fields. The features were those of stromal endometriosis. The endometrium was of the early secretory type, and a benign cystic endometrial polypus was present which contained mucoid material. The cervix showed chronic cervicitis with no evidence of malignancy. The patient was referred for a full course of deep X-ray therapy, and when last seen on 10 January 1969 she was well, with no evidence of recurrence.

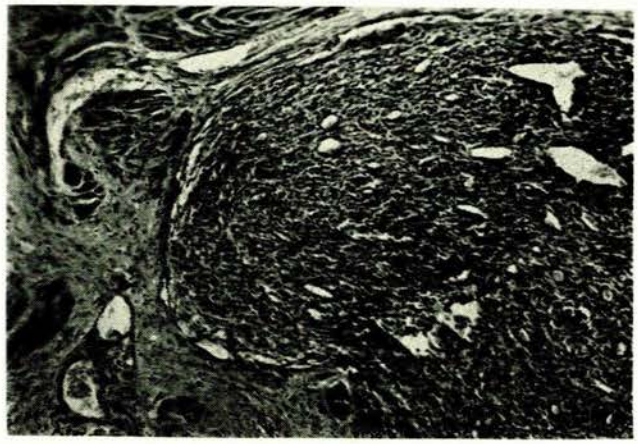

Fig. 3. Low-power magnification of a section of the tumour of case 2.

Fig. 4. High-power magnification of a section of the tumour of case 2.

DISCUSSION

Histiogenesis

It is not surprising that a host of names have been appended to this rare neoplasm because of the uncertainty of its origin, variations in the histological pattern and its unpredictability.

Its highly vascular microscopic pattern suggested the source of origin to be from blood-vessels[2-5] and hence the terms 'haemangiopericytoma' and 'angioblastoma'. Doran and Lockyer[2] apparently first described this tumour as a peri- and endothelioma as far back as 1908.

Origin from totipotential cells is favoured by several authors,[6-12] the new tissue arising from indifferent cells or myometrial stromal cells.

Stromal endometriosis so closely resembles internal endometriosis (adenomyosis) with the accent on stromal cells and the presence of endometrial glands, that Hunter *et al.*[13,14] gave it its present popular designation.

With the passage of time, however, more frequently reported tumour recurrences, even after considerable intervals of time after operation, have been noted and have indicated a more sinister significance to this disease. Such names as 'stromatosis',[7] 'stromatoid mural sarcoma',[8] 'endolymphatic stromal myosis',[15] 'endometrial sarcoma'[16] and others attempt to pinpoint the true nature of the malignancy of this new growth.

Browne[17] has no doubt about the malignancy of this neoplasm, and this view received support from the following facts: (*i*) The growth may arise after the menopause, unlike ordinary endometriosis; (*ii*) it does not necessarily undergo regression after removal of the ovaries; and (*iii*) there is a high percentage of recurrence after operation for removal of the entire growth. One might also add the unpredictability of recurrence after irradiation of the pelvis, unlike ordinary adenomyosis.

Pathology

Macroscopic appearances. The uterus was enlarged to a varying degree in all reported cases. As a rule, only one wall is occupied by a single large neoplasm, which bulges subserosally. Alternatively, there may be multiple fibromyomatous-looking tumours (stromal nodules),[18] either circumscribed or coalescent, varying from a few centimetres in diameter to a larger size, and again localized to one wall. The second type of nodules are usually solid in consistence, whereas the larger ones show degenerative change and are softer and cystic.

Bisection of the uterus almost always reveals a much-distorted, thick-walled organ, especially with a single large growth, and an enlarged distorted cavity caused by submucosal bulging with intramural extensions. Degenerative cystic polypoid formation is commonly seen in association with submucous tumours. Kraus[15] maintains this to be suggestive of stromal sarcoma which infiltrates the myometrium.

Norris and Taylor[18] noted that with stromal nodules the tumour mass on the cut surface bulged above the adjacent myometrium and endometrium, as in simple fibromyomata, and was often clearly demarcated from surrounding tissue in contradistinction to the more malignant variation. The latter was not clearly separated and often infiltrated myometrium and other tissue. The isolated or coalescent nodules appeared as pink or light yellow masses with haemorrhagic areas compared with cystic areas in larger single neoplasms.

Haynes and Taylor[19] describe these tumours in the freshly cut specimen as protruding from the cut surface and they are markedly accentuated by squeezing the uterus. After being stored in fixative these protrusions persist as worm-like structures. Robertson *et al.*[12] vividly describe the specimen as looking like a 'well-worn Turkish towel'. Projections from the cut surface do not take place if the uterus is first stored in preservative before bisection of the specimen. The worm-like structures are firm and elastic and when grasped by forceps recoil or can sometimes be pulled out from the myometrium.[19] When the neoplasm is large these structures cannot be pulled out easily from the myometrium, and in some non-frankly sarcomatous types they appear to push aside rather than infiltrate the myometrium which contrasts sharply in colour and texture from the tumour mass.

Norris and Taylor[18] stress that larger tumours without demarcation more often than not have infiltrated adjacent muscle and connective tissue.

Haynes and Taylor[19] noted that the cervix is often invaded by new growth and in one-third of cases the broad ligament is involved in that there are cord-like extensions along the course of blood-vessels to the fallopian tubes and ovaries and rarely to the vagina and urinary bladder.

Microscopic appearance (Figs. 1 - 4). Haynes and Taylor[19] described the typical picture of stromal endometriosis as a regular pattern of myometrium interspersed with areas of compact sheets of densely-staining cells resembling those of the endometrial stroma, sometimes in continuity with the stroma of the basal zone of the endometrium and even in continuity with the stromal elements forming the polypoidal protrusions into the uterine cavity. They maintain that endometrial glands are rarely found in combination with these marauding masses of stromal cells and as a rule they appear to be within lymphatics, in veins or in tissue spaces where they may herniate into a blood-vessel.

Hunter *et al.*[13,14] observed, on the other hand, the not infrequent presence of gland-like structures in typical instances of stromal endometriosis; a finding which they maintain bridges the gap between pure adenomyosis on the one hand and pure stromal endometriosis on the other. Similarly Norris and Taylor[18] found gland-like structures typical of endometrium in as many as 26% of their cases.

Kraus[15] described a similar picture, but also noted a prominent, uniformly distributed connective tissue framework in which small vessels ramify through the tumour in the majority of cases, characterizing its benign appearance.

Jensen *et al.*[16] also stress an overabundance of well-formed vascular channels to be an integral part of the diagnostic picture. Recurrence even many years later retains essentially this benign picture. Sarcomatous versions lack this prominent connective tissue support and circumscribed margins of the less aggressive counterpart. Infiltrating margins extend into the myometrium so that the tumour might blend with myometrium. Mitotic figures in these instances are numerous.

Norris and Taylor,[18] who examined 53 specimens of stromal endometrial neoplasms, classified them into 2 main groups: non-infiltrating and infiltrating. Non-infiltrating stromal endometrial tumours were called stromal nodules which manifest regular cell patterns which are remarkably constant and well circumscribed, with 'pushing' benign-looking margins between muscle bundles (Figs. 1 and 3). The myometrium is never infiltrated or the lymphatic or blood system invaded at the periphery of the neoplasm. On an average there were 2 mitotic figures per 10 high-power fields, significant of its benign character.

Infiltrating tumours were subdivided into further subgroups: (*i*) endolymphatic stromal myosis, and (*ii*) stromal sarcoma. The former group was of the same cell pattern as in the stromal nodule type of tumour, with 'pushing' margins, but with a tendency to infiltrate normal tissue. At the periphery of the new growth the cells extended irregularly between muscle bundles and along vascular spaces. The bulk of the tumour was extravascular, but in

every instance tumour cells protruded into lymphatic spaces at the periphery. Invasion of the blood system and prominent mitotic activity was evident in some of these cases but usually never more than 10 per high-power field.

The basis of separation between these 2 subgroups, according to Norris and Taylor,[15] was the degree of cell mitotic activity and orderliness or such activity with a mitotic count of more than 10 per 10 high-power fields. Clinical behaviour also was more sinister with the latter type (see below).

Jensen and co-authors[16] noted foci of hyaline degeneration in 40% of 15 neoplasms examined. Occasionally osteoid tissue was seen and in 6 instances gland-like structures were noted deep within the neoplasm.

Diagnosis

Stromal endometriosis is indistinguishable clinically from uterine fibromyoma. The true nature of the disease is usually revealed only after microscopic investigation of the removed uterus or tumour recurrence following previous operation.

The age of the patient when the first symptoms of the disease were revealed was most commonly in the forties. Rarely the condition has been described in postmenopausal women. Parous women are usually affected and young nulligravidae rarely so, though Norris and Taylor[15] reported such an instance in a 17-year-old girl, and Park[8] a woman between 21 and 25 years of age.

In 2 instances sinister rapidly-growing tumours were described after previous apparently simple multiple myomectomy, both within a time interval of 12 - 24 months. The first occurred in a 26-year-old nulligravida recorded by Hunter *et al.*[13] with recurrence after 12 months. She is still alive after 28 years in spite of recurrence. The second case in the literature is reported in this present paper, at the age of 32 years.

More often than not excessive bleeding with clotting occurring over a prolonged period of time was recorded due to marked enlargement of the uterus, distortion of the cavity and not infrequently the presence of endometrial polypi. Anaemia was hence a frequent accompaniment of the disease. Norris and Taylor[15] also reported 3 cases in which there was no menstrual upset at all.

An endometrial cast which microscopically revealed blood clot and stromal cells was passed on 2 occasions in case 1. This finding might be an important diagnostic aid, in spite of a usually uninformative curettage.

Pain of a continuous nature was a most constant feature, usually localized to the lower abdomen due to an enlarged tender uterus.

Enlargement of the uterus was invariably discovered on routine abdominal and vaginal examination, it being usually irregular in outline and appearing to be studded by multiple 'fibroids', or a single symmetrically enlarged organ.

Diagnostic curettage was as a rule non-informative, the one and only exception being a 59-year-old woman reported by Hunter *et al.*[13] Curettage revealed friable material which histologically showed stromal cells.

Even with direct inspection of the enlarged uterus at laparotomy, stromal endometriosis is never suspected, because of its close resemblance to fibromyoma.

In the majority of instances quoted in the literature the condition was diagnosed after previous hysterectomy or myomectomy with recurrence in the pelvis years later.

Treatment

There is no question that the treatment of choice for stromal endometriosis would be total ablation of the uterus and adnexa. Generally, however, the diagnosis is not made pre-operatively and one usually believes one is dealing with benign myomas. A revaluation of the case would, of course, be necessary under such circumstances.

Norris and Taylor[15] maintain that if the cervix is left behind, local recurrence is almost inevitable in that part of the uterus. Where stromal nodules were present they found that no such recurrence had occurred in their cases.

In endolymphatic stromal myosis removal of the ovaries in addition to hysterectomy made no difference to the ultimate prognosis compared with the excision of the uterus alone, because of the unpredictability of the disease.

In frank stromal sarcoma the outlook was always more serious as far as recurrence and survival were concerned, even with complete removal of the uterus and its appendages.

Henderson[7] considered stromal endometriosis to be radio-insensitive because of the maturity of the neoplasm.

Park,[8] in a review of the literature in 50 patients with this disease (which he preferred to call stromal mural sarcoma), found the results of surgery alone compared with surgery and radiotherapy to be no different in terms of recurrence and survival.

He also stressed that initial tumour radiosensitivity was not necessarily followed by cure. In 2 instances in which response to radiotherapy was dramatic at first, massive recurrence followed $11\frac{1}{4}$ and $9\frac{3}{4}$ years later. In case 1 of this present paper a similar dramatic response was noted after massive recurrence, the patient being alive and well without pelvic manifestation of the disease 13 years later.

It would appear, therefore, that irradiation of the pelvis should be instituted postoperatively in all instances of stromal endometriosis, irrespective of the histological picture, because of the unpredictability of response to such treatment.

Prognosis

The outcome of individual cases of stromal endometriosis is difficult, or even impossible, to forecast because of the chronic nature of the disease and its unpredictability.

In the past, many cases were classified as sarcoma but did not prove to be as lethal as expected. On the other hand, in lesions which were obviously 'benign' histologically, there was no guarantee against recurrence. Also, spread at operation does not necessarily mean a rapid fatal outcome.

There have been reports of local dissemination and visceral metastases as long as 28 years after operation. In one such instance quoted by Hunter *et al.*[13] a patient was alive and well 28 years after a second operation for recurrence involving the colon.

Park[8] reviewed 43 cases of what he termed stromal mural sarcoma and reported 5 deaths as a direct result of the disease.

Jensen *et al.*[16] recorded that 4 out of 15 patients with endometrial sarcoma died as a direct result of the lesion. Four out of 10 patients treated initially by these authors by hysterectomy with removal of both ovaries were alive, 3 without recurrence after 7 - 13½ years and one with recurrence after 7 years. When hysterectomy alone was done 3 were in good health after 4 - 30 years and 1 had died after recurrence. In 1 of 2 women who had undergone hysterectomy followed by postoperative radiation there were no signs of the disease after 9 years, and the other died of unrelated causes. Two of 4 women with recurrence in the pelvis died as a result of the disease after attempts had been made to surgically remove the growth in addition to subsequent irradiation.

Norris and Taylor[18] discussed survival rates in 53 cases with stromal endometrial tumours and formulated their rough guide of the outcome according to certain pathological criteria.

(a) *Survival rates according to tumour contour*: (*i*) Tumours with 'pushing' margins and with non-infiltration (stromal nodules) have an excellent prognosis. Thus in 16 of 18 women with this lesion recurrence after complete surgery was not established. Two women died from other causes.

It should be emphasized, however, that because of the unpredictability of the disease and in spite of the histological appearances the prognosis should always be guarded.

(*ii*) In neoplasms with infiltration of muscle and connective tissue 16% had died at 5 years out of 35 patients. At 10 years as many as 24% had not survived.

(b) *Survival rates according to mitotic activity*: With mitotic activity of 2 per 10 high-power fields and 'pushing' margins with cells similar to the normal endometrial cell there was 100% survival at 5 years. With mitotic activity of 10 or less per 10 high-power fields, as in endolymphatic stromal myosis with 'pushing' margins and infiltration, there was an actuarial survival rate of 100% at 10 years, even though recurrence had been found locally or in distant fields; after 12 years this rate was 95%. With mitotic activity in excess of 10 per 10 high-power fields, as in stromal sarcoma—of which there were 15 samples—the actuarial survival was only 55%. Only 4 women were alive and free from the disease. Seven had died and another 4 were living with tumour recurrence.

Similarly Evans,[20] Kimbrough[21] and Novak and Anderson[22] attempted to formulate a prognosis on the basis of mitotic activity. They found a mitotic count of less than 5 per 20 high-power fields gave a generally good outlook. The prognosis became progressively less favourable as more mitoses appeared.

Novak and Woodruff,[23] in a more recent series of cases, assessed the prognosis on the basis of mitosis in the 'worst' cases and noted the following results (Table I):

TABLE I. RESULTS OF NOVAK AND WOODRUFF[23]

Mitosis count	*No. of cases*	*Survival rates*	
		1 year	*5 years*
2 - 5/high-power field	18	100%	77%
6 - 10/high-power field	8	63%	38%
10 + /high-power field	3	0%	0%

(c) *Survival rates in relation to tumour size*: Norris and Taylor[18] noted that the larger the tumour in the infiltrating variety, the greater the frequency of recurrence. When the neoplasm was less than 4 cm., even in the infiltrating type recurrence thus far had not been discovered.

Recurrence after previous apparent simple myomectomy in the only 2 cases noted in the literature (i.e. including case 1) was highly malignant, both reasserting themselves within 2 years.

SUMMARY

Stromal endometriosis, a rare stromal endometrial neoplasm, is briefly discussed. The pathological and clinical features, treatment and prognosis are outlined with particular reference to previous literature.

Two cases of the disease are described, the first of which was of interest for the following reasons:

(*i*) Manifestations of a highly malignant new growth first appeared soon after multiple myomectomy for what appeared to be uncomplicated fibroids in spite of a relatively 'benign' microscopic picture of the subsequently removed uterus. This type of case is only the second of its kind to be reported in the English literature, under these circumstances.

(*ii*) An endometrial cast was passed after myomectomy which microscopically revealed only stromal endometrial elements, which should be a guide for a more accurate diagnosis of stromal endometriosis.

(*iii*) The dramatic response to irradiation in a seemingly hopeless secondary invasion, with survival without recurrence for 13 years.

From the evidence presented we believe that this neoplasm should be regarded as a malignant one, or potentially so, mainly because of its clinical unpredictability, even though microscopy envisages a chronic benign disease.

I wish to thank Prof. C. J. Uys for the histology reports in case 1, and Drs H. Rifkin and A. S. Peden for the histology report in case 2 as well as the photographs.

ADDENDUM

Most recent reports on case 1 revealed that she is well, without evidence of recurrence of her neoplasm, in January 1969, i.e. almost 14 years after operation.

REFERENCES

1. Casler, De W. B. (1920): Surg. Gynec. Obstet., **76**, 197.
2. Doran, A. H. G. and Lockyer, C. (1908): Proc. Roy. Soc Med., Obstet. Gynaec., 25.
3. Stout, A. P. and Murray, M. R. (1942): Ann Surg, **116**, 26.
4. Pedowitz, P., Felmus, L. B. and Grayzel, D. M. (1954): Amer. J. Obstet. Gynec., **67**, 549.
5. *Idem* (1955): *Ibid.*, **69**, 1309.
6. Goodall, J. R. (1940): J. Obstet. Gynaec. Brit. Emp., **47**, 13.
7. Henderson, D. N. (1946): Amer. J. Obstet. Gynec., **52**, 1000
8. Park, W. W. (1949): J. Obstet. Gynaec. Brit. Emp., **56**, 755.
9. Symmonds, R. E. and Dockerty, M. B. (1955): Surg. Gynec. Obstet., **100**, 232.
10. Symmonds, R. E., Dockerty, M. B. and Pratt, J. H. (1957): Amer. J. Obstet. Gynec., **73**, 1957.
11. Cope, E. (1958): J. Obstet. Gynaec. Brit. Emp., **65**, 58.
12. Robertson, T. D., Hunter, W. C., Larson, C. P. and Synder, C. A. (1942): Amer. J. Clin. Path., **12**, 11.
13. Hunter, W. C., Nohlgren, J. E. and Lancefield, S. M. (1956): Amer. J. Obstet. Gynec., **72**, 1072.
14. Hunter, W. C. and Lattig, J. (1958): *Ibid.*, **75**, 258.
15. Kraus, F. T. (1967): *Gynecologic Pathology*, p. 235. St Louis: C. V. Mosby.
16. Jensen, P. A., Dockerty, M. B., Symmonds, R. E. and Wilson, R. B. (1966): Amer. J. Obstet. Gynec., **95**, 75.
17. Browne, F. J. (1950): *Postgraduate Obstetrics and Gynaecology*, 1st ed., p. 137. London: Butterworth.
18. Norris, H. J. and Taylor, H. B. (1966): Cancer (Philad.), **19**, 755.
19. Haynes, M. and Taylor, C. W. (1962): *Gynaecological Pathology*, p. 167. London: J. & A. Churchill.
20. Evans, N. (1920): Surg. Gynec. Obstet., **30**, 225.
21. Kimbrough, R. A. (1934): Amer. J. Obstet. Gynec., **28**, 723.
22. Novak, E. R. and Anderson, D. F. (1937): *Ibid.*, **34**, 740.
23. Novak, E. R. and Woodruff, J. D. (1967): *Novak's Gynecological and Obstetric Pathology*, 6th ed., p. 241. Philadelphia: W. B. Saunders.