DIAGNOSIS AND TREATMENT OF CHORIOCARCINOMA

by

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The incidence of choriocarcinoma varies from 1 in 271 (Hasegawa) to 1 in 40,000 pregnancies (Hertig). In our hospital during the past 6 years (1954-59) there were 27 cases of choriocarcinoma and 79,896 deliveries, including abortions, giving an incidence of 1 in 2,958. The average age of these patients was 29 years (range 17 to 47 years) and average parity 3.7 (range 0-VIII). There was no relation between parity or age groups and this condition.

The diagnosis of choriocarcinoma was based on clinical examination, biological tests and pathological study of the tissue removed at biopsy or operation. In each case there was history of vaginal bleeding subsequent to last pregnancy. The interval between pregnancy and onset of symptoms ranged from 3 weeks to 3 months in over 2/3 of our cases and, in one, the last delivery was 25 years ago and 2 years had elapsed after menopause (Gupta). Eleven were preceded by vesicular mole, an equal number after abortions and 5 were after full-term delivery (about 40 per cent followed molar pregnancy; 40 per cent after abortions and 20 per cent after full-term labour Table I). Irregular fever and offensive vaginal discharge was also complained of by about 1/3 of the cases (Table II). Some patients who de-

TABLE I

Preceding Pregnancy and Choriocarcinoma

	No. of cases	Per cent	Novak & Seah (74 cases)	A. Sison (70 cases)
Hydatidiform mole	11	40.75	39.2%	62.85%
Abortion	11	40.75	37.8%	24.28%
Full-term delivery	5	18.5	23.0%	10.0%
	27			

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Read at 11th All India Obstetrics and Gynaecological Congress, Calcutta, January 1961.

TABLE II

Choriocarcinoma — Symptoms

	No. of cases
Irregular vaginal bleeding	27
Offensive vaginal discharge	8
Irregular fever	7
Pain lower abdomen	5
Chest pain and cough	5
Haemoptysis	4
Mass descending per vaginam	1

monstrated pulmonary metastases complained of chest pain, cough or haemoptysis.

Among the clinical signs, the most common finding was a bulky unusually soft uterus in an anaemic patient (Table III). Most of them required blood transfusion to correct anaemia. In 8 cases, the cervix was open and in five a polypoidal growth simulating submucous fibroid polyp was noted. Two cases were initially misdiagnosed as incomplete abortion and in one there was inversion of the uterus with vascular growth seen at the vulva (Fig. 1). In two patients (37 and 48 years of age) the cervical growth resembled carcinoma of the ectocervix and the mistake was realised only after hormonal and histologic studies. Nodules over the anterior vaginal wall, mostly suburethral in location were noted in eight. One 40 year old patient (Case No. 23) had a total hysterectomy for hydatiform mole and was readmitted only 25 days later with a vaginal metastatic deposit.

TABLE III

Choriocarcinoma — Signs

	No. of cases
Anaemia	16
Bulky uterus	23
Submucous fibroid polyp (?)	5
Incomplete abortion (?)	2
Inversion uterus	1
Carcinoma cervix (?)	2
Skin nodule	1
Vaginal nodules	8
Pulmonary secondaries (radiological)	10

Hormonal studies are helpful in the diagnosis of choriocarcinoma as well as in the follow-up for early detection of secondaries. In 25 cases, the male frog test was done with the morning specimen of urine from these patients (Table IV). In 21 it was positive, and negative in four cases. Most of them were positive with undiluted urine or with 1 in 100 dilutions. Only in one it was positive even in dilutions of 1 in 1500. Of the four negative ones, a positive result was obtained in three by concentration method using 60 ml. of urine and in one it remained

TABLE IV

Choriocarcinoma — Male Frog Test

Before operation		After operation			
Positive	Negative	2 to 3 months		6 months & over	
		Pos.	Neg.	Pos.	Neg.
21	4	5*	13	3**	4

* Except one all died in 3 months.

** All died in a year.

negative even though the pulmonary deposits were increasing as shown radiographically, and she died ultimately. In one case, it was positive repeatedly after removal of the primary growth and no clinical or radiological evidence of secondaries was made out; however, shortly before her death, 18 months later, pulmonary secondaries were evident.

Only cases where a histologic diagnosis of choriocarcinoma was made have been considered in this study. The previous sections which were available were reviewed and 2 cases of invasive moles, mistaken for chorionepithelioma, were rejected as formed villi were noted after careful examination. Diagnostic currettage was not always decisive and in three it proved negative. In each case, diagnosis was confirmed after study of the sections of the primary growth and in case No. 23 from the resected vaginal nodule. The primary tumor in the uterus was most often a purplish haemorrhagic mass appearing as a large single growth (Fig. 2) or as multiple nodules of different sizes. It was invariably embedded in the myometrium of an enlarged uterus though the extent of the myometrial invasion was variable; in six it had penetrated up to the peritoneal surface (Table V) and in four it had extended into the cervix. In seven cases, the ovaries were enlarged and cystic but typical bilateral lutein cysts were seen only in three of them.

The microscopic diagnosis in these cases depended on total absence of preserved villi, the invasion of the myometrium by irregular columns of trophoblastic cells, both Langhan's and syncytial, and wide areas of necrosis and hemorrhage in the muscle. Thus a definite histological diagnosis could be more confidently made after hysterectomy than from curettings, as in the former instance a more thorough study of the different parts of the tumor was feasible. Zones of round-cell collections, indicating the reaction of the muscle to the invasion, were usually present at the edge of the invading tumour and at the periphery of the necrotic areas. In the better preserved parts of the tumour, not only there were no formed chorionic villi but the syncytial and Langhan's cells were irregularly intermingled. We found this feature of considerable diagnostic help, as the orderly arrangement and clear demarcation of the two zones was always found among the cells that enveloped the normal chorionic villi or those found in even the most active moles. The proportion between the two cells varied widely, though the predominance of one cell type in some parts of the tumors was often manifest. Among the syncytial cells, giant cells —unusually large multinucleated masses—were seen only occasionally. The arrangement of the Langhan's

TABLE V

Choriocarcinoma — Sites of Lesion

	No. of cases
Endometrium and myometrium	22
Peritoneum involved	7
Cervix	4
Vagina	8
Ovary	5
Bladder	2
Bowel	1
Pelvic lymph node	1

cells in small clusters or in larger well-formed alveoli was noteworthy in a few cases. Thus the vast majority of cells in a tumour could be identified as being either syncytial or Langhans in type. We rarely encoutered undifferentiated cells that could not be labelled in either category, for their presence is considered by some to be an index of anaplasia and so of malignancy of a tumour.

Treatment

Panhysterectomy was done in two-thirds of our patients (Table VI) and in two of these, it was followed by irradiation. The case with inversion of the uterus was treated by vaginal hysterectomy and right salpingo-oophorectomy. In case No. 23, the vaginal nodule was subjected to diathermy excision. No treatment was given in two advanced cases.

The extent of the growth prior to surgery influenced the prognosis (Table VII). In patients where the growth was limited to the uterus, the prognosis was better than in those where it had spread to other pelvic viscera or to the lungs. The mortality in this series was 14 out of 27 patients, 51.85%. Of the remaining, 7 have been traced and are now healthy. Six patients could not be traced; two of these, when last seen three months following the operation, showed evidence of secondaries and may be presumed to be dead. If

TABLE VI
Choriocarcinoma — Treatment

Type of treatment	No. treated	No. dead		No. alive		Not traced
		Six months	Six months	1-2 years	Over 2 years	
Panhysterectomy	23	8	3	1	5	4 + 2*
Vaginal hysterectomy with bilateral salpingo-oophorectomy	1	1	—	—	—	—
Removal of secondary nodule	1	—	—	—	1	—
Curettage only	2	2	—	—	—	—
	27	11	3	1	6	6

* Had secondaries when last seen.

TABLE VII
Extent of Lesion and Result

Nature of lesion	No. treated	No treatment	Result		Not traced
			Dead	Alive	
Restricted to uterus only—peritoneum free	12	—	3	5	3 + 1*
Spread outside uterus but only in pelvis	6	1	5	1	1*
Pulmonary metastases	7	1	6	1	1

* Had secondaries when last seen.

they be included, the mortality in this series is 59.25%.

Discussion

The clinical diagnosis is only presumptive if there is a preceding history of recent molar abortion and vaginal bleeding in an anaemic patient in whom bimanual examination shows a bulky uterus. Additional finding of a vascular vaginal nodule or radiographic finding of pulmonary deposits may make it almost certain. Still, a metastatic mole cannot be ruled out. A clinical diagnosis should always be supported by a biological test and invariably by histologic examination of the tissue removed at operation. Smalbraak emphasises the superiority of the biologic test as a diagnostic aid over the histologic examination, though we agree with Novak and Seah and also Hunter and Dockerty that histologic diagnosis is by far the most certain of all the diagnostic procedures. We believe that the chorionic gonadotrophins excreted in urine of patients suffering from choriocarcinoma are less in amount than in cases of hydatidiform mole. It is also interesting to see that in four of our cases the biologic test was negative by ordinary method and three of them ultimately died, the remaining one showed pulmonary deposits three months later. The negative biologic test, in proved cases of choriocarcinoma, have been reported in over 30 cases collected from the literature (Smalbraak). This is explained by presence of a fibrinoid layer surrounding the comparatively less vascular growth, or the predominant cell type of tumour being of the syncytial pattern. The primary growth may give a negative biological test but after its removal the secondaries may produce enough hormone to give a positive reaction. This was noted in one of our cases where the male frog test was negative even by concentration method before the removal of the primary tumor, but when the patient was seen three months later for haemoptysis the test was positive. In our study, no definite correlation between histologic cell pattern of the tumour and its hormonal production was noticed.

The diagnostic value of curettings from the uterus depends on the site and extent of the tumour included in the biopsy material sent for study. If this shows only necrotic tissue with few isolated trophoblastic cells, a post-abortal picture is simulated, for the great resemblance between very necrotic villi amidst blood and the necrotic parts of the tumor (really the myometrium) is often misleading. Thus in three cases, from the curettings, "necrotic villi" was the report; however, a definite diagnosis of choriocarcinoma was established after hysterectomy, prompted by clinical and biological findings. If a small growth is located near the fundus of the uterus or deeply embedded in the myometrium, a curettage may fail to obtain material sufficient for a certain diagnosis. A second factor that renders a preoperative diagnosis difficult is the striking similarity, in morphology and behaviour between normal trophoblast and malignant tissue. Familar features of malignancy like anaplasia, cellular pleomorphism, nuclear hyperchromatism, mitosis or

invasion into tissue spaces and vascular channels are the normal properties of the trophoblast. Yet, if sufficient material is available for study from the curettings, a presumptible and strongly suggestive diagnosis could be offered in most cases; in this series such a diagnosis was possible in sixteen cases from a curettage. Should a diagnostic curettage be always done, when choriocarcinoma is suspected? The dangers of perforation and hemorrhage are mentioned; many also point out the risk of provoking a dissemination from a tumor, so prone to rapid metastasis. Yet, despite its pitfalls and limitations and even the rather exaggerated element of risk we would strongly advocate that a proper curettage must be done before surgery; for the diagnostic value of a uterine curretage far outweighs its apparent shortcomings. Otherwise, many an avoidable and unnecessary hysterectomy will be the result.

Treatment of choice is panhysterectomy. Conservation of the ovaries in the belief that they are rarely the foci for secondaries and that oestrogens may help in prevention or regression of metastases is a risky practice. Five out of 27 cases in this series showed secondary deposits in the ovaries. In one fatal case of choriocarcinoma with inversion of the uterus where the left tube and ovary were spared at the primary operation, she had to be operated again hardly three months later for ovarian and lymph node metastases. Choriocarcinoma, unlike other cancers, spreads rapidly by the blood stream and before local recurrence could develop, the patient may die because of spread to distant organs. Therefore there is no use in post-operative irradiation to the pelvis in these cases. Hormonal therapy, both with androgens and oestrogens in large doses, has been tried in advanced cases. Androgens have not been found useful but oestrogens reduce the hormonal production by the tumour and may give but temporary relief. In two cases with pulmonary secondaries, oestrogen therapy was given a trial but was given up for want of response in one and toxicity in the other. We have no experience with the use of antimetabolites in the treatment of this cancer.

The mortality in choriocarcinoma varies from almost cent per cent (Ewing) to as low a figure as 28.57% (A. Sison) or even 5% (Mathieu). In this series it was 51.85%. If the survival rate is high the diagnosis is usually looked upon with suspicion and a thorough review of the histologic material by a competent pathologist is called for.

Summary

1. Twenty-seven cases of choriocarcinoma seen during the past 6 years (1954-1959) in the Hospital for Women and Children, Madras, have been reviewed. Its incidence in this institution is 1 in 2,958.

2. The clinical, biological and pathologic diagnostic criteria in this disease have been briefly discussed.

3. There is no correlation between histologic cell type of the tumour and positive biological test.

4. Most certain diagnosis can be made only from histologic examination of the specimen removed at operation and not from diagnostic curettings only. The presence of

formed chorionic villi on histologic study is against a diagnosis of choriocarcinoma.

5. The treatment of choice for choriocarcinoma is panhysterectomy.

6. The mortality rate in this series is 51.85 percent.

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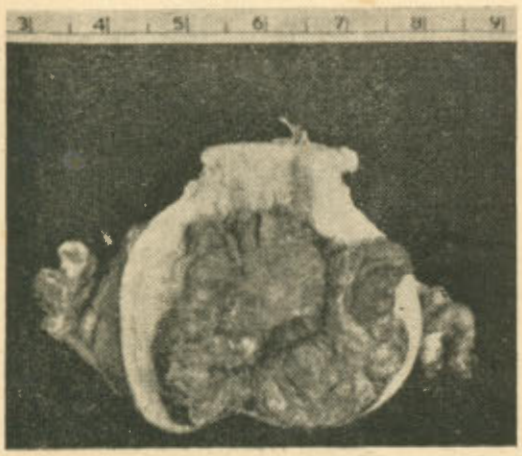

Fig. 1
Choriocarcinoma, a large tumour was felt as a polypoid mass, through the cervix.

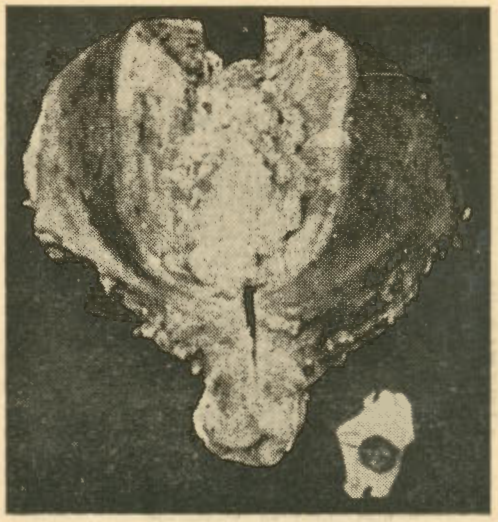

Fig. 2
The uterus with a vesicular mole and the choriocarcinomatous vaginal nodule, which appeared within a month after hysterectomy (Case No. 23).

Fig. 3
Choriocarcinoma causing inversion of the uterus.

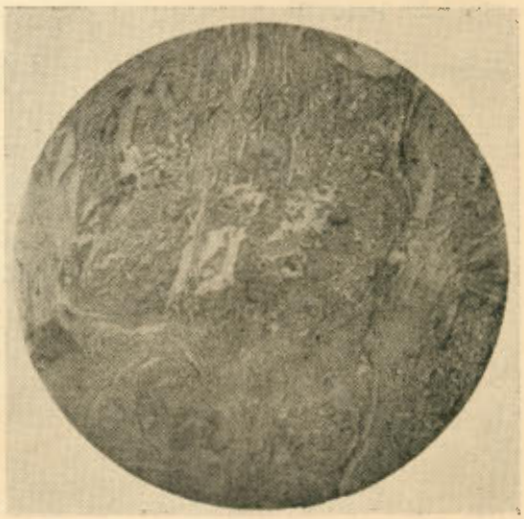

Fig. 4
A large mass of Langhan's cells, showing well-formed alveolar grouping (x 48).

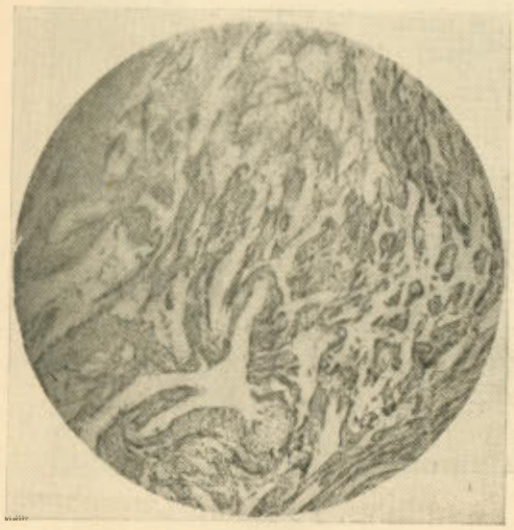

Fig. 5
Both types of cells are seen closely intermingled in this part of the tumour (x 48).

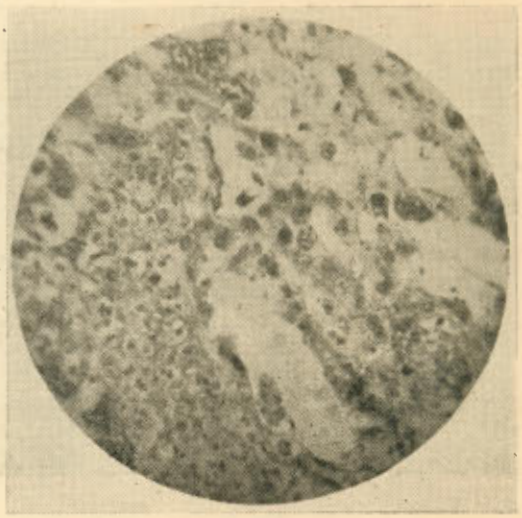

Fig. 6
A high power view of the tumour to show the morphology of the Langhan's and syncitial cells (x 240).