CHORIOCARCINOMA: A REVIEW OF CURRENT CONCEPTS BASED ON THE SINGAPORE EXPERIENCE

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Choriocarcinoma is a disease of long recognition and the subject of much research. Nevertheless, certain aspects of its natural history and clinico-pathological correlation are imperfectly understood. These deficiencies in knowledge are attributable to the great rarity of the disease in those communities where major research work has been conducted. Under those circumstances, authorities such as Hertig and Novak had to place heavy reliance on retrospective studies of pooled pathological material with clinical information supplied from many diverse sources. Such methods are liable to a certain element of unavoidable error and are, at best, incomplete.

At the Kandang Kerbau Hospital, Singapore, opportunities for the study of choriocarcinoma and related conditions are unique. During the past five years a prospective study has been conducted on over 400 moles and 57 cases of malignant chorionic tumours. The present review is based on the knowledge gained from this experience.

INCIDENCE

There appears to be a marked geographic variation in the incidence of choriocarcinoma. Park (1962) reported only one death from choriocarcinoma in 70,000 live births in Great Britain and Northern Ireland. While Hertig (1950) in America gave an incidence of one case in 40,000 pregnancies. In Hong Kong, however, the tumour incidence was 1 in 1,331 hospital deliveries at the University Hospital (Chan 1962). Acosta-Sison (1962) reported an incidence of 1 in 1,382 pregnancies in a hospital practice in the Philippines. In Singapore the incidence is approximately 1 in 5,000 hospital deliveries. The incidence of this tumour in the Far East is apparently several times that in the West.

AETIOLOGICAL CONSIDERATIONS

According to the Singapore experience, choriocarcinoma is preceded by hydatidiform mole in 70 per cent, abortion in 20 per cent and third trimester pregnancy in 10 per cent. The term "abortion" usually implies a retrospective diagnosis based on the patient's history and seldom on histological evidence. Not infrequently the expulsion of a mole is reported by patients as "abortion". Therefore, if a more searching history were obtained and careful examinations of all abortion material were carried out routinely, more cases of choriocarcinoma would be found to have been preceded by hydatidiform mole.

In an extensive Joint Project for Study of Choriocarcinoma and Hydatidiform Mole in Asia (1959) conducted by a team of American investigators with the collaboration of Asian patholcgist and clinicians from 1948 to 1957, no causal relationship could be demonstrated between the occurrence of choriocarcinoma and specific geographical, racial or cultural factors. In Singapore, however, where there are three major ethnic groups, (Chinese 75 per cent, Malaysians 13 per cent, Indian/Pakistanis 8 per cent) the Indian and Pakistani women appear to be somewhat less susceptible to the disease. In a series of 57 cases only one was Indian, whereas deliveries among this racial group amount to some 8 per cent per year.

In a recent study in Singapore (Tow, 1964) 200 consecutive cases of hydatidiform mole were followed up since 1959. Advancing age and parity were found to significantly increase the incidence of malignant change (Table 1). The rate of malignancy at 40 years and over was $3\frac{1}{2}$ times that of women below that age. For cases under 40 years of age rising parity (3 and over) increased the rate of malignancy to a similar extent.

Among Asian investigators, it is a common observation that choriocarcinoma affects the lower socioeconomic section of the population. The underlying aetiological factor eludes identification but an attractive theory is that there is a breakdown of the body defence due to some

nutritional defect. Acosta-Sison whose experience in this field is unrivalled considers the lack of high class protein to be an important factor.

PATHOLOGICAL CONSIDERATIONS

The natural history of choriocarcinoma is schematically presented in Fig. 1. The foetal chorion has inherent malignant properties, namely invasion of maternal decidua and vascular transportation. Normally the local invasion of maternal tissues comes to an abrupt end with the expulsion of the placenta in labour, while the phenomenon of embolic transportation, first demonstrated by Schmorl in 1893, appears to be a frequent, symptomless and innocuous accompaniment of pregnancy.

In the neoplastic process the trophoblastic epithelium proliferates independently and at the expense of the mesodermal villous core. The disease may affect any pregnancy, molar or otherwise, but the ultimate product is identical, *i.e.*, a malignant tumour of trophoblast with little or no villus formation. Such a histological picture represents the fully fledged neoplasm called "choriocarcinoma" (Fig. 2). The speed of malignant transformation is extremely variable. It may occur simultaneously with a pregnancy or follow soon afterwards, but in the majority of cases a considerable latent interval intervenes before the disease becomes clinically manifest.

If the malignant process affects a molar pregnancy, the tumour may become very destructive in the pelvis and display a marked tendency to metastasize. It may perforate through the uterus or infiltrate the broad ligaments and precipitate an acute abdominal emergency requiring surgical intervention at an early stage while villous elements have not yet been overgrown by the epithelial proliferation. Histologically, then, the growth is labelled "chorioadenoma destruens" (Fig. 3). If the victim is not treated in time, death ensues from internal haemorrhage and, less commonly, also from widespread metastases. Surgical intervention with removal of the primary growth is curative in about half the cases. In the other half metastases will have occurred and will require further treatment in order to forestall progression to choriocarcinoma.

From the foregoing account of the natural history of trophoblastic neoplasms, it would appear that both choriocarcinoma and chorioadenoma destruens are manifestations of one common underlying pathological process of trophoblastic malignancy at different stages. Chorioadenoma represents an earlier and less malignant stage while choriocarcinoma represents the fully fledged malignancy. This viewpoint is supported by the observation in Singapore that chorioadenoma destruens followed hydatidiform mole by an average interval of 6 weeks while choriocarcinoma followed it by many months (Fig. 1). Although less malignant, chorioadenoma is nevertheless liable to metastasize to lungs, brain and vagina, in a manner no different from choriocarcinoma.

If these arguments are acceptable, then it is not unreasonable to amend the nomenclature accordingly. All malignant trophoblastic lesions should be called "choriocarcinoma." The villus-containing chorioadenoma should be called "villus choriocarcinoma" and the non-villous growth "avillous choriocarcinoma." These terms are a more accurate expression of the underlying pathological process and would solve practical difficulties in diagnosis.

Primary choriocarcinoma begins in the uterus, infiltrating and destroying uterine muscle and adjacent pelvic tissues. In nearly half the cases the growth is wholly intramural and beyond the reach of the curette, thus limiting the value of diagnostic curettage. The growth is characteristically haemorrhagic and nodular, and although most do not attain to a large size, an occasional case may reach the size of a second trimester pregnancy.

Metastatic spread takes place early and by way of the blood stream to the lungs, vagina and brain, but no tissue is exempt (Hou, P.C. and Pang, S.C., 1956). These deposits grow in the new environment and destroy like the primary tumour. Most often death ensues from metastatic involvement of the brain and lungs, but haemorrhagic sequelae of uterine destruction or intraperitoneal catastrophes are not uncommon.

In about a third of cases, extensive metastatic choriocarcinoma exists in the presence of a normal healthy uterus. This phenomenon may be explained on the hypothetical basis of local resistance, which in the uterus is able to overcome the tumour invasion. Spontaneous regression of choriocarcinoma is a rare phenomenon given prominence in the literature. In practice it

TABLE 1

MALIGNANCY IN 200 MOLES RELATED TO AGE AND PARITY (TOW, 1964)

AGE	MOLES	MALIGNANCY	PER CENT
40 years & over ...	30	10	33.3
39 years & under ...	170	16	9.4
„ Para 3 & over	91	13	14.3
„ Para 2 & under	79	3	3.8
OVERALL ...	200 cases	26 cases	1

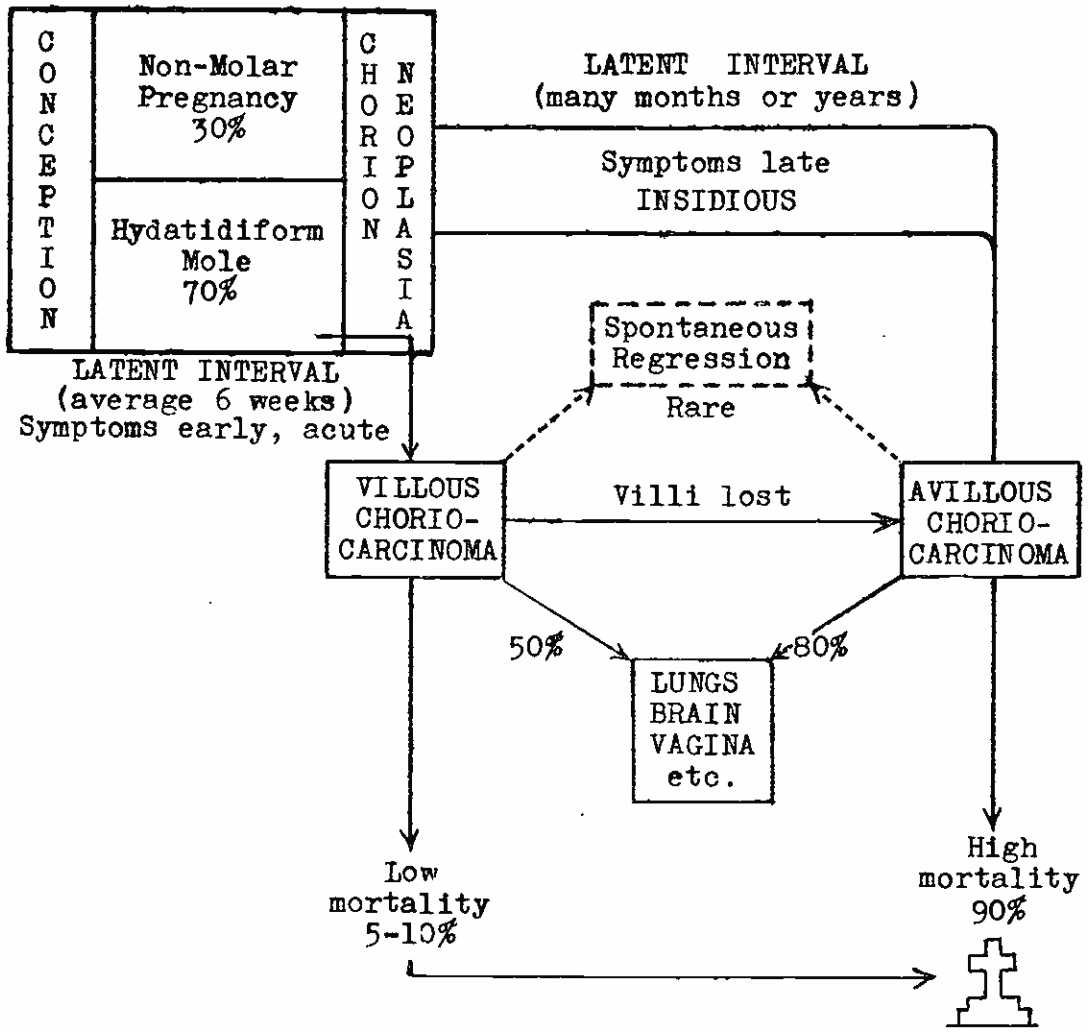

Fig. 1. Schema showing pathogenesis and natural history of choriocarcinoma based on the Singapore experience, 1964.

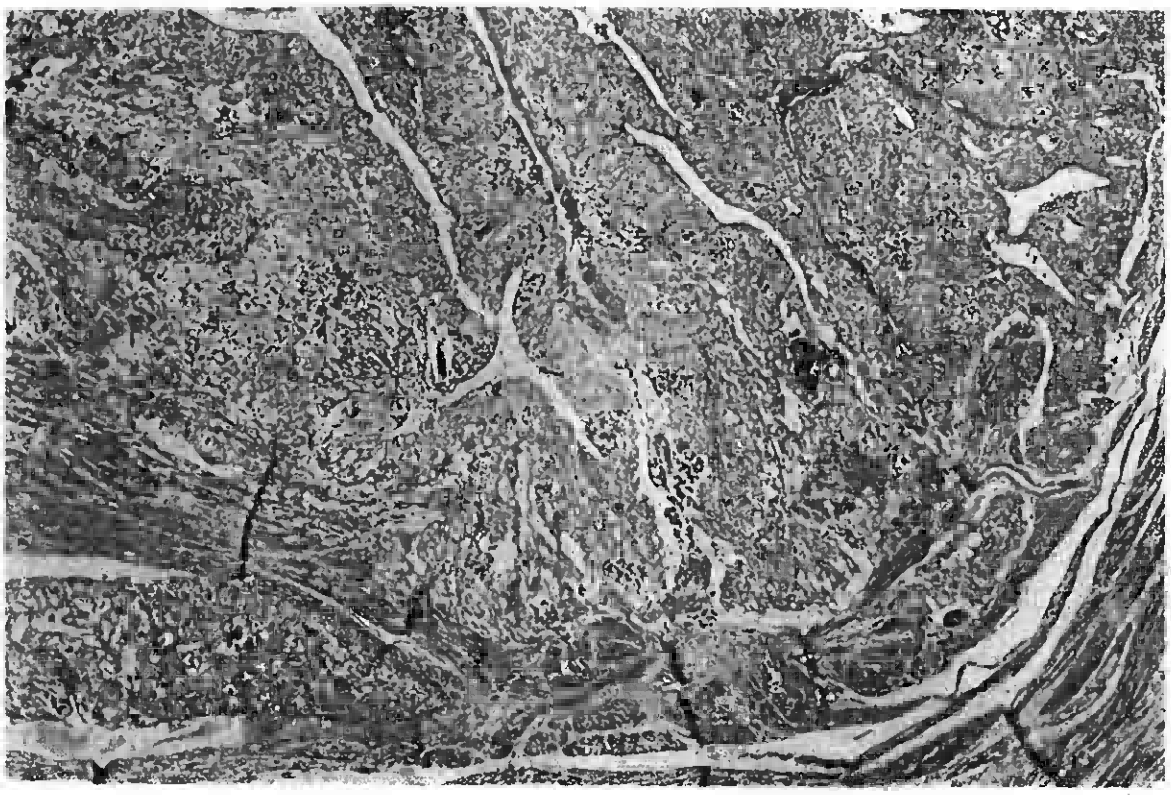

Fig. 2. Avillous choriocarcinoma in the uterus, (x 90).

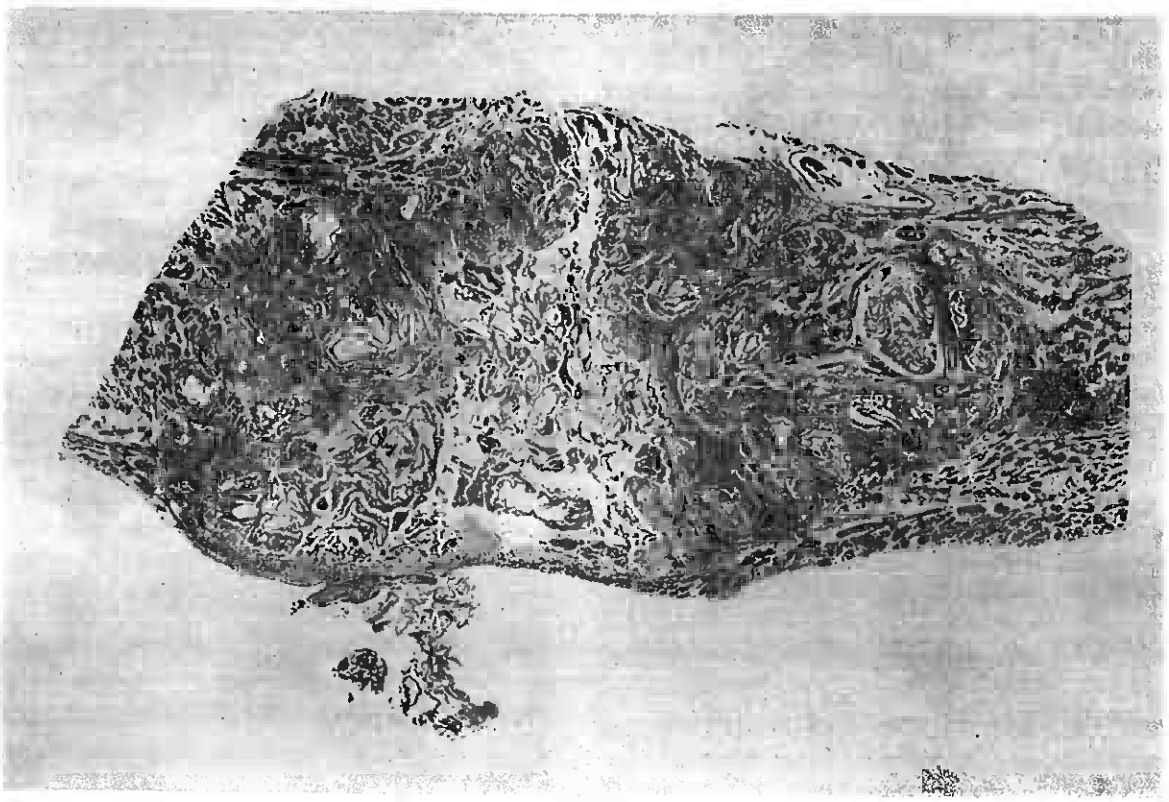

Fig. 3. Villous choriocarcinoma invading uterus, with perforation, (x 5).

must not be relied upon in the hopeful expectation of a cure.

CLINICAL MANIFESTATIONS

Choriocarcinoma may manifest itself by its (a) local, (b) hormonal and (c) metastatic effects. In any given case one or a combination of effects may be present. Not infrequently clinical manifestations are slow in appearing and many cases are not diagnosed until the disease is well advanced and widely disseminated. Unlike hydatidiform mole, choriocarcinoma is not complicated by pre-eclamptic toxaemia.

(a) Local Effects

In the majority of cases, an intrauterine growth is present, causing uterine enlargement, although in the early stages this may not be appreciated. Being a destructive and haemorrhage-provoking lesion, abnormal uterine bleeding presents as the leading symptom. In the follow-up of hydatidiform mole, abnormal uterine enlargement or subinvolution with irregular bleeding are ominous signs. In those cases where there is no primary growth in the uterus episodes of amenorrhoea rather than bleeding are likely. The uterine enlargement may simulate fibromyoma and cancer of the uterine body. The tumour may perforate the uterus and cause internal bleeding. Where it has extended into the broad ligaments and adjacent pelvic structures it may present as a broad ligament haematoma or pelvic haematocele or abscess. If internal bleeding occurs a picture of ruptured ectopic gestation presents.

(b) Hormonal Effects

The tumour liberates chorionic gonadotrophin and the use of pregnancy tests is of utmost value in diagnosis. Any one of the many pregnancy tests now available may be used. Of the biological tests, the method of Delfs (1959) using mouse uterine weight is probably the most accurate for quantitative estimations. On the other hand, the recently introduced immunological tests are more convenient and practical. A positive response, especially a persistent one following molar pregnancy, or its reappearance after a period of quiescence, is indicative of possible malignancy. The differential diagnosis is from normal pregnancy and hydatidiform mole. Occasionally a negative biological response, is obtained even in the presence of an actively growing tumour. In such a case, cross-checking with an immunological test is indicated.

The effect of chorion gonadotrophin on the ovaries may be seen in the formation of multiple theca lutein cysts with suppression of ovulation. Thus the clinical detection of ovarian cystic enlargement is of serious import. With the suppression of ovulation, there is interruption of the normal menstrual cycle with prolonged periods of amenorrhoea in cases where the endometrium is not affected by the growth.

(c) Metastatic Effects

Choriocarcinoma is characterised by early dissemination by the blood stream, leading to metastases in over 80 per cent of avillous growths and 50 per cent of villous growths. The sites in order of frequency are lungs, brain and vagina (Figs. 4, 5, 6). Such is the tendency for early spread that not infrequently the first

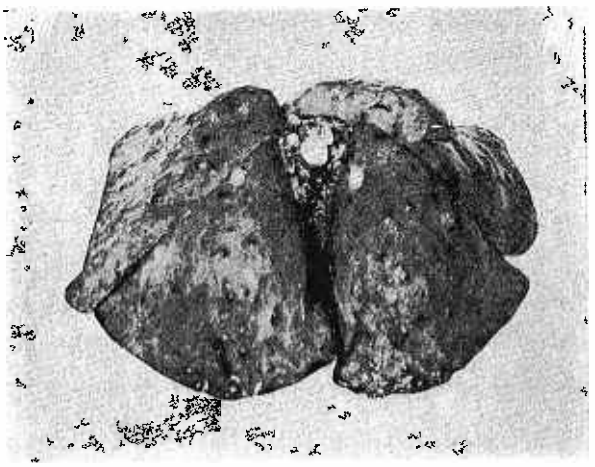

Fig. 4 Multiple deposits in lungs.

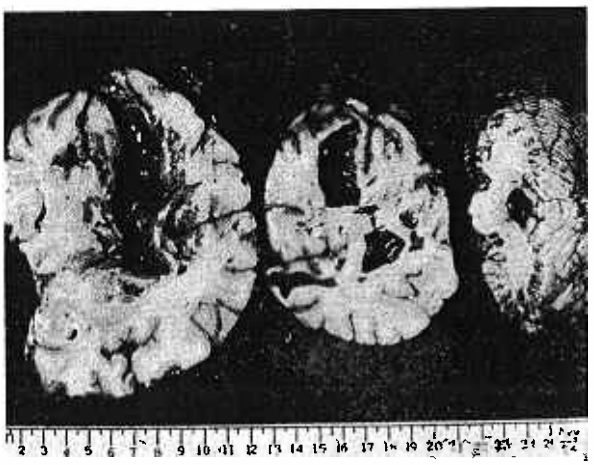

Fig. 5. Brain involvement with haemorrhage.

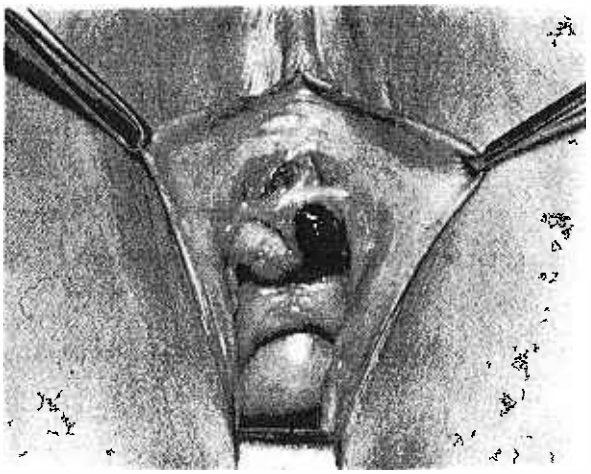

Fig. 6. Nodule in vaginal introitus, a typical site.

evidence of disease is precipitated by a secondarily implanted growth in one of the common situations listed, or indeed, in any other site of the body.

In the vagina, the growth most often appears as a dark haemorrhagic or bluish nodule in the anterolateral aspect of the introitus. It may be single or multiple, and varies in size from a pea to a large walnut. When necrosis and breakdown set in, the lesion becomes a source of considerable blood loss and the patient may be exsanguinated. Metastases in the lungs lead to cough and haemoptysis, and in advanced cases to pulmonary insufficiency and corpulmonale. Radiographically, the growth may assume the appearance of any pulmonary disease. The typical early lesion appears as multiple nodules in both lung fields, scattered throughout all zones, as would be expected from haematogenous spread (Fig. 7). Occasionally, if a radiograph is obtained very early, miliary lesions may be seen. More advanced growths appear as "cannon balls" (Fig. 8) or complete consolidation of large areas of the lung. Other radiographic appearances may be diagnosed as "pulmonary eosinophilia," "atypical basal pneumonia," and "bronchopneumonia" (Fig. 9). Pulmonary metastases may give a picture of right-sided cardiac failure. The rupture of a surface nodule leads to bleeding into the pleural cavity simulating "pleural effusion" (Fig. 10).

Not uncommonly, the patient presents with intracranial haemorrhage, with varying degrees of paralysis and coma. In the presence of such clinical manifestations, the outlook becomes grave. The end may be swift and sudden or it may be delayed for weeks or months, but from it there is no escape.

Finally, the disease may present as an obscure intra-abdominal lesion such as hepatitis, liver abscess or hepatoma. It may give rise to an acute abdomen by bleeding from the site of secondary implantation in any abdominal organ, such as liver, kidney, bowel, omentum or spleen.

DIAGNOSIS

The diagnosis of choriocarcinoma can be very elusive especially in clinics where the lesion is rarely seen. The clinical features and methods of presentation vary so widely as to afford little real indication of the disease at an early stage, unless of course a history of molar pregnancy is obtained. In the absence of such a clue, the diagnosis will depend on a clinical awareness of the possibility of its existence, careful physical, radiographic and hormonal examination.

The histological diagnosis hinges on the demonstration of massive aggregates of trophoblasts with scanty or complete absence of villus formation in pathological material obtained by curettage, biopsy or hysterectomy. Typically, these cells are found in the depths of the host tissues causing extensive necrosis and haemorrhage.

In cases where no pathological material is available, as when the uterus obtained at hysterectomy contains no growth, diagnosis will have to be based on the history, and clinical, radiographic and hormonal findings. If death occurs, confirmation may then be obtained at autopsy.

TREATMENT

a) Prophylactic

In the Singapore experience, 13 per cent of hydatidiform moles turn malignant. Since the majority of choriocarcinomas are preceded by moles, the management of the latter would play an important role in the reduction of this malignancy. Hysterotomy is commonly practised because of the teaching that it is superior to "D and C" in preventing subsequent malignancy. Such teaching and practice are quite erroneous. Experience has shown conclusively that hysterotomy does nothing whatever to reduce the risk of

RADIOGRAPHIC APPEARANCES OF CHORIOCARCINOMA IN LUNGS

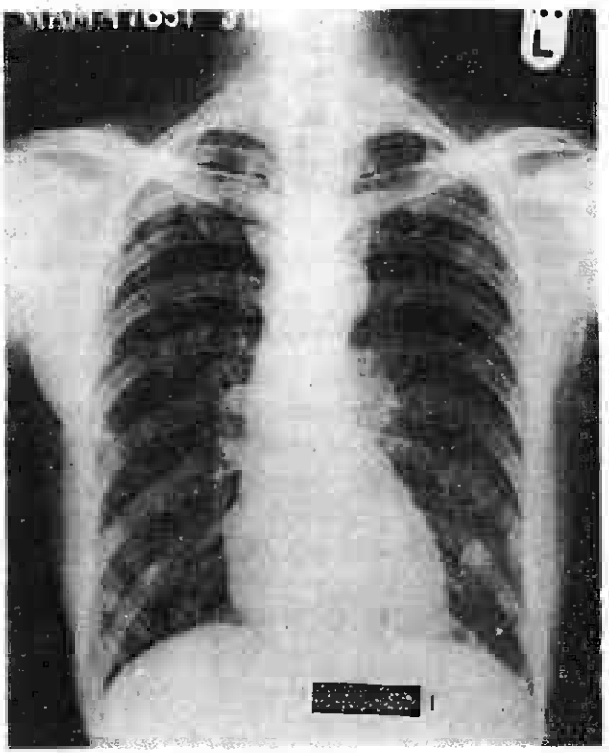

Fig. 7. Multiple nodules.

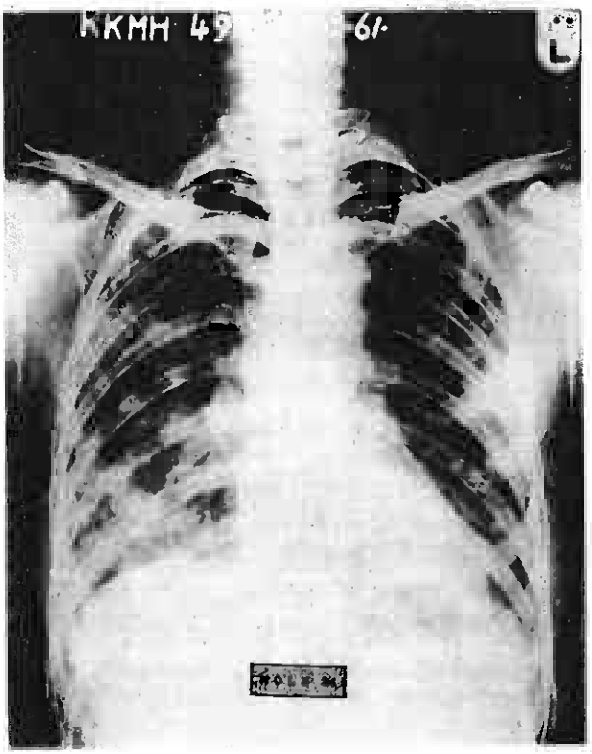

Fig. 9. Atypical pneumonia or "pneumonitis".

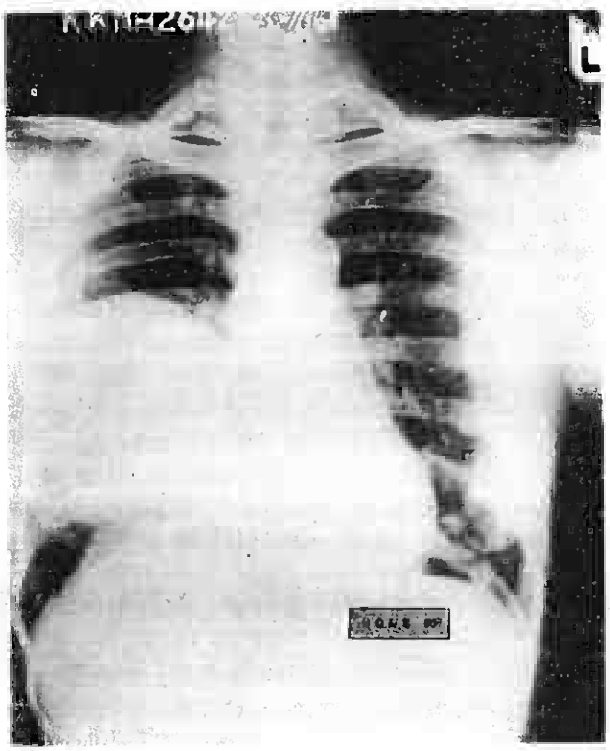

Fig. 8. Large "cannon ball".

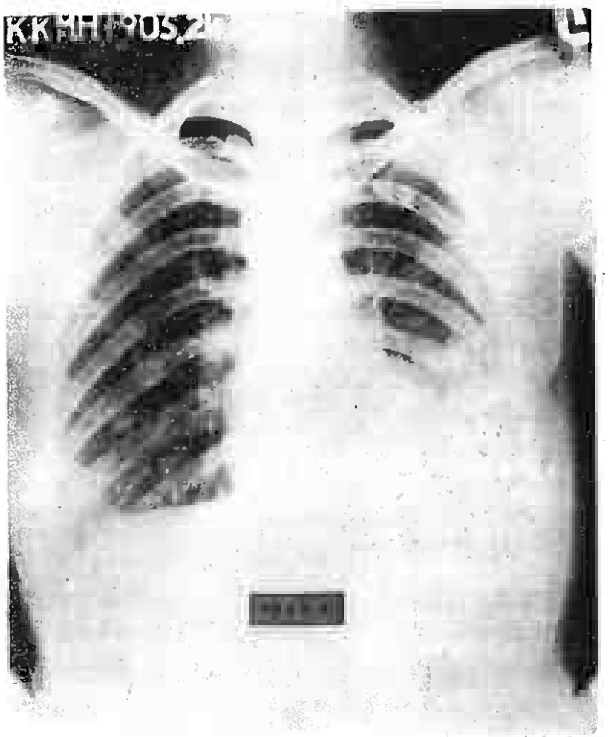

Fig. 10. Haemothorax simulating pleural effusion.

malignancy. It should be abandoned. If the uterus has to be evacuated, a simple "D and C" irrespective of uterine size is to be preferred. The operation is safe, simple and time-saving, and is to be preferred to hysterotomy from all points of view.

Hysterectomy, on the other hand, has a definite place in preventing malignancy. As earlier mentioned, cases of hydatidiform mole turning into choriocarcinoma almost always go through a latent interval before malignancy and effective tumour dissemination set in. Hysterectomy performed at the time of molar pregnancy or immediately afterwards has proved effective in preventing malignancy and/or dissemination in the great majority of cases. This prophylactic measure carries minimal risk in competent hands and its advisability must be viewed in the light of malignancy rates of 33.3 per cent in patients over 40 years, and 14.3 per cent in those under 40 years and are para 3 or more (Table I). Hysterectomy should be advised for these two groups of women. Only those who must have more children, *i.e.* young women in the para 0-2 group should be allowed to retain their uteri.

For those who are conservatively treated, careful supervision with regular clinical, radiographic and hormonal assessments must be continued for at least 3 years. Successful pregnancy may supervene but this event is no proof of cure or safeguard against subsequent malignancy as some people believe. It is likely that the prophylactic administration of a cytostatic agent will help to reduce the risk of undetected and future malignancy. Initial trials with methotrexate for this purpose appear to be satisfactory.

The value of histological grading of hydatidiform moles in prognostication of future malignancy and hence in indicating the advisability of prophylactic hysterectomy has been a matter of keen controversy. On the one hand, the Boston school led by Hertig (1956) have devised various histological criteria for assessing the malignant potential of each individual mole. On the other hand, Novak (1958) and others were unable to place firm reliance on these microscopic features for predicting malignancy.

During the past 5 years about 400 patients with hydatidiform mole have been treated and followed up at the University Department of Obstetrics and Gynaecology in Singapore. In the light of this experience it has become evident that as a method of predicting malignancy, morphological criteria based on aborted molar tissue are of variable accuracy and limited value for clinical application. If malignancy has already set in or is imminent, then the molar tissue will reveal microscopic features of malignancy. For long term prognostication, however, there is no reliable and constant relationship. The need for hysterectomy, therefore, must be decided on grounds other than morphology.

b) Curative

Surgery is the first choice in curative treatment. This should be employed wherever feasible, *e.g.* where the uterus contains a growth and is operable. Secondary deposits in the vulva and vagina, if not too extensive should be excised. Deposits in the lungs confined to a limited area should be considered for surgical extirpation if a good response to chemotherapy is not obtained. In cases where the whole tumour-bearing area is excised, a cure may be expected. This in fact is not an uncommon outcome if diagnosis and treatment are instituted early. There is no evidence to support the theory that the removal of a primary growth would cause the regression of metastases. Such belief is contrary to clinical experience. It may help, however by eliminating a source of further metastases. When performing hysterectomy in women of reproductive age, every effort should be made to conserve healthy ovaries, including those enlarged by lutein cysts. To sacrifice ovaries in young women is a serious mistake.

Before the advent of chemotherapy, metastatic choriocarcinoma carried a mortality of close to 100 per cent. In recent years a number of chemotherapeutic agents have been used with favourable results, such as 6-mercaptopurine, chlorambucil, vincaleukoblastine, methotrexate and actinomycin-D The drug most widely used is methotrexate either alone or in combination with 6-mercaptopurine or actinomycin-D. The survival rate obtained with metastasized tumours ranges from 40 to 70 per

cent. (Hertz et al, 1961; Chan, 1962; Bagshawe, 1963).

The regime employed in the treatment of metastatic chorionic tumours has been described in detail by Hertz and his associates (1958) at the National Institutes of Health in America. Methotrexate should be given to the patient in hospital in 5-7 day courses, using about 20 mg. per day in 4 divided doses by the oral route. A check on toxic side effects is kept by means of clinical observation and estimation of the total leucocyte count. Response is assessed by the radiographic appearance of pulmonary metastases, shrinkage of palpable or visible deposits and by means of pregnancy tests. Therapy should continue until all evidences of disease have regressed after which a further 3 courses should be given as a safeguard against reactivation.

The chief toxic effects are anorexia, gastrointestinal upset, stomatitis, urticarial rash, bone marrow depression and alopecia. Most of the subjective discomfort disappears within a week and leucopenia within two weeks from the completion of a course. With due care, fatal toxicity is a rare complication.

A favourable response is seen in the clearing up of metastatic deposits, subjective feeling of well-being, relief or cor pulmonale if present, negative pregnancy test or a falling titre. In cases of amenorrhoea, menstruation returns. If methotrexate should prove ineffective, an alternative cytostatic agent such as 6-mercaptopurine or actinomycin-D should be used. At least three courses should be given before one should decide that a particular drug is ineffective.

In the University Department of Obstetrics and Gynaecology in Singapore, 57 cases of chorionic malignancies have been treated over the past 5 years. Surgery was performed in every operable case. Metastatic spread was present in 40 cases; of these, 11 were avillous choriocarcinomas seen before chemotherapy was available and 10 have died (9 per cent survival). After the introduction of chemotherapy in 1960, 18 metastatic choriocarcinomas were treated, with 7 survivals (38.8 per cent). Ten cases of villous choriocarcinoma with metastases were treated, with 100 per cent survivals. The overall survival among cases of metastatic choriocarcinoma treated with chemotherapy is therefore about 60 per cent, the periods of survival ranging from a few months to over three years.

SUMMARY

Choriocarcinoma is a malignant neoplasm of the foetal trophoblast characterised by a marked tendency to metastatic spread and if diagnosed late, a usually rapid and fatal course. Its high incidence among low socioeconomic groups has led to the suggestion of a nutritional factor in its aetiology. Seventy per cent of avillous choriocarcinomas are preceded by hydatidiform mole, the remaining cases by non-molar pregnancies. Thirteen per cent of moles become malignant. The risk of malignancy increases with age and parity.

The basic pathology in choriocarcinoma is trophoblastic proliferation, with destruction of host tissues and metastatic spread by the blood stream. The chief sites of disease are uterus, lungs, brain and vagina, but no tissue is exempt. In about a third of cases, metastatic choriocarcinoma exists in the absence of a primary growth.

Moles progressing along a malignant course if diagnosed early, will be seen to have a villous pattern. The conventional terminology for such a growth is "chorioadenoma destruens." More advanced malignancies lose their villous pattern and are then labelled "choriocarcinoma." The two lesions are nevertheless manifestations, at different stages, of one common underlying disease process, and should be called "villous choriocarcinoma" and "avillous choriocarcinoma" respectively.

Clinically, both villous and avillous choriocarcinoma manifest local, hormonal and metastatic effects. Their modes of presentation are extremely varied but the salient diagnostic features are abnormal uterine bleeding and/or enlargement, evidence of local tissue destruction and distant metastases, and a positive pregnancy test. A history of molar pregnancy is of great diagnostic significance.

The prophylaxis of choriocarcinoma lies in the performance of hysterectomy in "risk cases" viz; cases of hydatidiform mole who are aged 40 and over, or para 3 and over. Hysterotomy is of no proven value in prophylaxis and should be abandoned in favour of a simple "D and C". Accurate prediction of malignancy in moles cannot be made on morphological criteria. These

criteria cannot be used to indicate the need for prophylactic hysterectomy.

Curative treatment relies primarily on early surgery with supportive chemotherapy for metastatic desease. In the latter condition, chemotherapy has revolutionized treatment and prognosis. It has raised the survival rate in metastatic choriocarcinoma from under 10 per cent to 40 - 70 per cent.

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