Papers and Originals

Recent Trends in Treatment of Choriocarcinoma

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World-wide interest has been focused on the successful chemotherapy of choriocarcinoma. Recent reports by Hertz *et al.* (1964) and Brewer *et al.* (1964) in the United States of America and by Bagshawe (1963) in the United Kingdom suggest that a high degree of success may be obtained with chemotherapy alone, and that hysterectomy adds little to the recovery rate and may in fact impair the response to chemotherapy. Hertz *et al.* and Bagshawe also stress the importance of treating patients in sterile units such as those at the National Institutes of Health, Bethesda, Maryland, and Fulham Hospital, London.

An attempt is made in this paper to evaluate the validity of the foregoing claims in the light of our experience in the past seven years.

Material and Method

During the period 1959 to 1966 80 cases of trophoblastic malignancy and over 500 cases of hydatidiform mole were treated in the University Unit at the Kandang Kerbau Hospital, Singapore, as part of a prospective study of trophoblastic diseases. This paper reports the experience and results obtained in the management of the 80 cases of trophoblastic malignancy up to June 1966. All cases have been managed under our personal supervision. Operation and necropsy specimens have been examined and classified by one of us (W. S. H. T.).

Definition, Diagnosis, and Classification.—Choriocarcinoma is defined as the presence of chorionic growth outside the normal bounds of the maternal decidua, with manifestations of malignancy. The diagnosis of malignancy was based on (a) the histological demonstration of massive aggregates of trophoblasts within the depths of the myometrium or in any extrauterine site associated with tissue destruction and haemorrhage, and (b) the radiological demonstration of persisting opacities in the lung fields consistent with metastatic choriocarcinoma and supported by a positive test for chorionic gonadotrophin. The classification adopted in the 80 cases was that advocated by Tow (1965). All chorionic malignancies were termed "choriocarcinoma" and prefixed by "villous" or "avillous," depending on the histological pattern. Cases which yielded no material for histological study were labelled "clinical choriocarcinoma." On this basis the cases were classified as villous choriocarcinoma in 27, avillous choriocarcinoma in 33, and clinical choriocarcinoma in 20.

Clinical Presentation

In 64 cases the disease occurred in association with or as a sequel to hydatidiform mole. It is likely that in the vast majority of these cases, if not all, malignancy was already present from the time of molar pregnancy, and those that presented as delayed sequelae had merely escaped diagnosis earlier.

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The manifestations of malignancy were uterine perforation with internal bleeding, or the effects of metastatic deposits in vagina, lungs, brain, and elsewhere. The latent interval between the event of molar pregnancy and the appearance of symptoms of malignancy varied from nothing to as long as 12 years.

In 16 cases choriocarcinoma was preceded by non-molar pregnancy. Most cases in this category had a rather prolonged latent interval of months or years before the appearance of malignancy. On the average it was certainly much longer than in molar pregnancy. The reason for this difference is that molar pregnancy serves as a warning and facilitates earlier diagnosis during the follow-up supervision. In non-molar pregnancy such follow-up naturally is lacking.

The chief symptoms of choriocarcinoma were attributable to disturbance of menstrual, cardiopulmonary, abdominal, and neurological functions. Many patients were afflicted with more than one symptom, though some were symptomless at the time of diagnosis. A precise mathematical analysis of the frequency of each symptom is difficult if not impossible. However, in broad terms menstrual disturbances were encountered in 55%, chest manifestations in 20%, "acute abdomen" in 15%, and neurological disorders in 10%.

Of the menstrual disorders three-quarters were irregular or excessive flow and one-quarter scanty or suppressed. Chest manifestations were cough, haemoptysis, and dyspnoea. About half were symptomless cases discovered on routine radiography. The small and early lesion is not radiographically demonstrable, but the presence of embolic arterial obstruction is seen in mild cardiac enlargement and increased vascular markings. Radio-opaque lesions take the form of "miliary" or "nodular" opacities, "cannon-balls," "patchy pneumonitis," and diffuse "cotton-wool" or "snowstorm" appearances. Bleeding from a ruptured surface lesion results in haemothorax formation simulating pleural effusion.

Acute abdominal symptoms were precipitated when a destructive growth ruptured on to the peritoneal surface and caused free bleeding. The organs involved were uterus, tubes, bowels, liver, kidney, and spleen.

Neurological symptoms due to cerebral involvement were invariably secondary to pulmonary metastatic disease. Intense headache, papilloedema, varying degrees of paralysis, and coma were the usual manifestations of intracranial growth.

The 80 cases from clinical, operative, and necropsy data are analysed in Table I.

TABLE I.—Sites of Metastases in 80 Cases of Choriocarcinoma (1959-66)

Site	Clinical and Necropsy		Necropsy (13 Cases)
	No.	%	
Lung	55	69	13
Uterus	52	65	8
Brain	22	27	11
Vagina	15	19	1
Others	10	12	6

Hormonal Tests in Diagnosis

The release of chorionic gonadotrophin by trophoblasts provides a convenient and unique measure of tumour activity for diagnostic purposes as well as for assessment of response to treatment. In Singapore the haemagglutination-inhibition test of Wide and Gemzell (1960) was introduced in October 1964 and has superseded the male toad test, which was found to give 50% false-negative results at chorionic gonadotrophin titres of 5,000 i.u./l. In the present series, only urines were used for the test. For inpatients first morning specimens and for outpatients fresh random samples were used.

Treatment

Surgery

The surgical procedures employed in treatment of the 80 cases were hysterectomy, excision of vaginal metastases, and resection of lung deposits.

Hysterectomy.—Total abdominal hysterectomy was performed 59 times—four times palliatively in cases with distant metastases before chemotherapy was available, 17 times as primary treatment for hydatidiform mole, and 38 times as a definitive therapeutic measure in choriocarcinoma. From these operations 45 uterine growths were removed. Hysterectomy was performed in patients who were surgically fit and whose uteri were thought to harbour a malignant growth. It was withheld in young nulliparous patients and in those with extensive metastases. There was no operative mortality or serious postoperative complication.

Excision of Vaginal Nodules.—Operable metastatic deposits in the vagina were excised. Of the 15 cases with vaginal metastases nine were subjected to such treatment. The remaining six were either too advanced for surgery or had regressed with chemotherapy.

Lung Resection.—Cases with solitary pulmonary opacities which did not resolve completely with chemotherapy were considered for surgery. The operation was performed on five patients in whom the lung growths appeared to be the only viable focus of disease. This proved to be a correct assumption in one case. A solitary viable growth was removed and the patient remains well. In another case the lung at operation was found to contain multiple nodules and only an excision biopsy was performed. In the remaining three cases solitary healed nodules were removed. There was no operative mortality.

Chemotherapy

Methotrexate and mercaptopurine were not available until September 1960 and intermittent supplies of actinomycin-D were available from January 1963. Two standard regimens of chemotherapy were used: (a) methotrexate 20 mg. and mercaptopurine 400 mg. daily for five to seven days, given in four divided doses by the oral route; this was used from September 1960 to May 1961, and again from January 1965 up to the time of writing. (b) methotrexate alone, in the same dosage, was used from June 1961 to December 1964. Actinomycin-D was used in cases which proved resistant to these regimens. The dosage was 0.5 mg. daily by the intravenous route for five days.

Chemotherapy was started as soon as a patient was fit, judged by the following criteria: haemoglobin concentration not below 12 g./100 ml., leucocyte count at least 4,000/cu. mm., and the patient was not dehydrated or toxic. After each course about two weeks were allowed for the patient to recover from toxic effects such as anorexia, anaemia, leucopenia, skin rashes, and lesions of the gastrointestinal tract. Antibiotics were given if there were signs of infection. Symptomatic treatment was

given as indicated. Anaemia and severe leucopenia were corrected by transfusions of fresh blood.

Patients under chemotherapy were treated in an open ward with other gynaecological patients. These wards were bright and airy. Daily wet-mopping of the floors maintained a reasonable state of cleanliness. Fatal sepsis due to chemotherapy was not encountered.

One course of preoperative chemotherapy was given before surgery to provide a "sterilizing" effect and minimize the risk of tumour dissemination. Surgery was carried out when the patient had recovered sufficiently from the toxic effects of chemotherapy.

Response to Treatment

Response to treatment was assessed by: (a) observing the size of visible growths in the vulva and vagina, or lesions demonstrable by radiography; (b) observing the general state of the patient; and (c) observing the titre of chorionic gonadotrophin excretion. Initially, the male toad test was used, but since October 1964 the haemagglutination-inhibition test alone has been used.

Results

Of the 80 cases 49 were cured, 30 died, and one was still under treatment. The criterion of cure was complete freedom from any evidence of disease for six months or longer. The 49 cures are related to the method of treatment in Table II. In 17 cases of localized uterine tumour and two cases of localized uterine and vaginal tumour surgical removal of the growths was 100% curative. Distant metastases were found in 61 cases. Of 36 treated with hysterectomy and chemotherapy 12 died, one was under treatment, and 23 were in a state of cure. Chemotherapy alone was employed in 13 other cases, resulting in six deaths and seven cures. Twelve cases with distant metastases did not have the benefit of chemotherapy and were treated with palliative measures, including surgical procedures. All 12 died from the metastatic growths.

TABLE II.—*Survival in Choriocarcinoma Related to Method of Treatment (1959-66)*

Tumour Extent	No. of Cases	Treatment	Deaths	Cure*
Uterus only	17	Total hysterectomy	0	17
.. and vagina ..	2	Excision of nodule	0	2
Distant sites involved	36	Total hysterectomy.		
		Chemotherapy (one case under treatment)	12	23
	13	Chemotherapy only	6	7
	12	No chemotherapy	12	0
Total ..	80		30	49

* Freedom from disease for six months or longer.

The 49 patients who received chemotherapy may be divided into three groups: 24 had methotrexate alone, with five deaths; 18 had methotrexate and mercaptopurine, with five deaths; and seven became resistant to methotrexate or methotrexate and mercaptopurine, and eventually received actinomycin-D. All seven in the latter group died. No apparent superiority was shown by any one chemotherapeutic regimen over another.

Cause of Death.—The causes of death in 30 cases, according to clinical and necropsy evidence, are shown in Table III. The cause of death was not ascertained in two cases.

TABLE III.—*Cause of 30 Deaths in Choriocarcinoma from Clinical and Necropsy Evidence (1959-66)*

Cerebral haemorrhage	23 cases
Pulmonary failure	4 "
Internal haemorrhage	1 case
Unknown	2 cases

Discussion

Chemotherapy has radically improved the prospects of cure in choriocarcinoma well beyond what may be achieved by surgery alone. Recent reports from Britain and America referred to earlier claim that chemotherapy alone yields better results than those of chemotherapy and surgery combined. In fact it is stated by Bagshawe (1963) and Hertz *et al.* (1964) that surgical measures such as hysterectomy may impair the response to chemotherapy and worsen the cure rate. These claims deserve careful study before hysterectomy is abandoned altogether.

The first observation to make is that the foregoing reports have come from specialized chemotherapy centres which receive referrals of highly selective material, including cases treated unsuccessfully by hysterectomy. It may be reasonably expected that in such cases the disease is more advanced than in cases referred without prior surgery. From this unintentional selection two groups would emerge: one with previous surgery and more advanced disease, and the other with no previous surgery and less advanced disease. Both groups are now subjected to chemotherapy. The comparison of the eventual results on this basis becomes highly prejudicial against the group with previous surgery.

A second observation is that these specialized centres do not receive referrals of the many cases successfully treated elsewhere with surgery and/or chemotherapy. Evaluations of therapeutic methods which fail to take these cases into account can hardly be fair or accurate. Furthermore, some of the cures credited to chemotherapy (Hertz *et al.*, 1964) were based on inadequate evidence of malignancy. Careful examination of the papers by Bagshawe (1963) and Brewer *et al.* (1964) also fails to reveal any convincing evidence against hysterectomy.

What evidence, then, is there in favour of hysterectomy? To conduct a prospective study of two statistically significant and comparable groups of cases is probably impossible. We must therefore approach the subject from an understanding of the pathological process. Choriocarcinoma begins in the pregnant uterus. The pregnancy may be molar as well as non-molar. Prophylactic measures designed to eradicate malignancy are applicable only to molar pregnancies, for obvious reasons. Prophylactic or primary hysterectomy when applied to two "risk groups" in molar pregnancy has been shown to be effective in reducing deaths from subsequent malignancy by 70% (Tow, 1966), though the malignancy rate itself was not reduced. This strongly suggests that malignancy in moles is probably present in the uterus from the beginning, though the ultimate clinical appearance may be delayed for varying periods of time. The two "risk groups" mentioned are women who have moles and are aged 40 or more, and younger patients who have had three or more children. These groups carry malignancy risks of 36 and 14% respectively (Tow, 1966). Routine prophylactic hysterectomy is likely to offer the best prospects of freedom from future trophoblastic malignancy and metastatic disease, though it does not eliminate the risk altogether.

In the case of suspected or diagnosed choriocarcinoma three factors determine the advisability of hysterectomy: the extent of the disease, the presence of a uterine growth, and the need for further child-bearing. If a localized uterine growth is present and there is no need for further childbearing timely hysterectomy may well be curative. Even if there are minor metastases in the lungs hysterectomy is still advisable if the uterine growth is large. Small intramural growths may be

identified by pelvic arteriography. Removal of the tumour mass eliminates once and for all the source of tumour emboli and thus aids the body defence mechanism. However, if the brain is involved by growth or if the lungs are extensively infiltrated, or if the patient is young and desires more children, then hysterectomy is contraindicated.

The above policy has been observed in the treatment of these 80 cases, and the results justify the practice (Table II). The therapeutic value of hysterectomy has been amply demonstrated.

Chemotherapy is the acknowledged mainstay in the treatment of metastatic choriocarcinoma and is useful even in apparently non-metastatic cases. Various regimens using methotrexate, mercaptopurine, and actinomycin-D have been evolved at Bethesda by Hertz *et al.* (1964). Success depends on careful assessment of response by a sensitive test for chorionic gonadotrophin—for example, the haemagglutination-inhibition test—so that therapy may be modified accordingly. If a tumour should prove unresponsive to one drug a change should be made early. Bagshawe, in a personal communication, reports favourable results with pelvic arterial perfusion in patients with disease mainly confined to the pelvis. An adequate therapeutic effect may be obtained with a considerable reduction of the dose, thus sparing the patient from many of the severe toxic side-effects.

Though the patients in Singapore were treated in open wards with other gynaecological patients, no cases of death from infection have been encountered thus far. Severe leucopenic crises have been successfully treated by transfusions of fresh blood. There is no evidence as yet to suggest that the cure rates are improved by isolation of patients in sterile units. This observation is of considerable practical importance because it means that cases of choriocarcinoma may be safely and successfully treated in a gynaecological unit with reasonable laboratory facilities.

Summary

Recent claims that hysterectomy is valueless and probably harmful in the treatment of choriocarcinoma are not supported by the evidence presented from Singapore. On the contrary, it has been demonstrated that timely hysterectomy in selected cases with tumours largely or entirely localized to the uterus is still a valuable therapeutic measure. Chemotherapy is shown to play a decisive part in the treatment of metastatic choriocarcinoma. No case of fatal sepsis has been encountered and good cure rates have been obtained without the aid of a sterile isolation chemotherapy unit.

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