below 40 who have had three or more children. This policy of prophylactic or primary hysterectomy has been followed, in treating hydatidiform mole, since November 1961. In a series of 31 cases of pulmonary chorion carcinoma following hydatidiform mole there were 12 deaths, all in patients who did not have primary hysterectomy.
Therapeutic: The therapeutic measures used were surgery and chemotherapy. The choice of surgery, i.e. hysterectomy, was determined by the extent of the disease and the need for further childbearing. If the pulmonary disease was already extensive or if further childbearing was an important consideration then hysterectomy was not performed. On the other hand, if the disease was mainly confined to the uterus and if future childbearing was not needed, then hysterectomy was undertaken.

Chemotherapy was used in 44 cases. In 11 cases chemotherapy was either not available or was refused. The standard course was methotrexate 20 mg and 6-mercaptopurine 400 mg daily for five to seven days. Therapy was not begun unless the patient was fit, i.e. general condition satisfactory, hæmoglobin concentration not less than 12 g % and leucocyte count at least 4,000/c.mm. As a rule, two weeks were allowed between courses for recovery from toxic side-effects. Cases going for surgery received one course of preoperative chemotherapy. Response was checked by periodic estimations of gonadotrophin and chest radiography. Three courses of chemotherapy were given after a negative titre had been obtained, in order to ensure complete eradication of trophoblasts which might perhaps be in a dormant state.

Results

Of the 55 patients, 30 have died, giving an overall survival rate of 45%. Table 1 shows the results related to the methods of treatment. Chemotherapy has increased the chances of survival from zero to nearly 60%. Prophylactic hysterectomy in the treatment of hydatidiform mole in 'risk groups' gave 100% survival. Hysterectomy did not improve the survival rate in pulmonary chorion carcinoma. This is in agreement with the experience of Hertz *et al.* (1964), Brewer *et al.* (1964) and Bagshawe (1963).
Cause of death: The causes of death in the 30 cases were as follows: cerebral hæmorrhage 21, pulmonary insufficiency 6, others 3.
Prognosis: The prognosis was largely determined by the extent of pulmonary involvement. Large 'cannon ball' lesions, multiple nodules filling both lung fields and extensive 'snow storm' lesions had a poor prognosis. Cerebral involvement was always a grave sign. Improved cure rates are possible with earlier diagnosis.

Table 1
Survival in pulmonary chorion carcinoma related to method of treatment (Kandang Kerbau Hospital, Singapore, 1959–66)

No. of cases	*Treatment*	*Cure●* *No.*	*%*
7	Prophylactic hysterectomy for hydatidiform mole; chemotherapy	7	100
13	Chemotherapy only	7	54
24	Hysterectomy; chemotherapy	11	46
11	No chemotherapy	0	0
55	All methods	25	45

● Freedom from all evidence of disease for six months or more

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Gonadotrophin Excretion, Pelvic Arteriography and Treatment in Post-molar Trophoblastic Disease

It is unusual to find evidence of trophoblast surviving after term delivery or early termination of normal pregnancy. By contrast, trophoblast commonly survives after evacuation of hydatidiform mole. Its location in the uterus, pelvic vasculature or lungs may not be definable but its presence is indicated by continued production of chorionic gonadotrophin.

This persisting trophoblast usually dies out spontaneously but Delfs (1959) using bioassays found that it was still present in more than 20% of 118 cases sixty days post-evacuation. The radioimmunossay for HCG-LH (Bagshawe *et al.* 1966) would possibly give a higher figure because it is more sensitive. After sixty days, spontaneous trophoblastic necrosis may still occur in some

patients but is not complete in all of them; the threat of malignant sequelæ presents a problem with important theoretical and practical aspects.

Arteriographic examination of patients with persisting post-molar trophoblast shows a high incidence of gross abnormalities which have been described by various workers (Borell *et al.* 1955, Cockshott *et al.* 1964) and our own observations will be presented in detail elsewhere (Brewis *et al.* 1967). These appearances have been ascribed to 'malignant trophoblastic disease' a description which has the disadvantage of implying a fatal prognosis if untreated. Unfortunately, the arteriographic abnormality, dramatic as it often is, does not indicate the future course of the disease. Benign post-molar lesions cannot be reliably distinguished from malignant ones. Gross arteriographic changes may regress spontaneously and minor abnormalities may be followed by progressive disease: arteriographic regression does not guarantee that total trophoblastic death has occurred or that progressive disease will not follow; successful chemotherapy may be accompanied by return to normal arteriographic appearances but this is not invariable and gross abnormalities may persist for months after tumour destruction is complete. The main value of arteriography is that it often provides good visual localization of a lesion whose presence is known but not anatomically defined. The demonstration of extrauterine tumour and the continuity of such a tumour with vaginal metastases may also be valuable.

Several factors have to be taken into account in deciding whether, when and how to treat. The longer the time interval after evacuation, the greater is the risk of overt malignancy and of cerebral metastases and the less certain the response to chemotherapy. Intervention may be precipitated by symptoms – uterine or vaginal hæmorrhage, abdominal or chest pain and dyspnœa. It may be acceptable to withhold treatment in the presence of one or two small pulmonary metastases provided other indications, such as a falling HCG titre, are favourable. But in patients with lung lesions the risks of intracranial spread are substantial. Where there is good histological evidence of chorion carcinoma, treatment should not be withheld. Such evidence is, however, uncommon in this group since the objective is often to avoid hysterectomy. Precise quantitative HCG assays provide invaluable information (Bagshawe & Wilde 1965): high values indicate large tumour masses; increasing values indicate the rate of tumour growth; falling values may allow continued observation. It is also relevant that prolonged follow up stresses not only patients but also hospital follow-up proficiency. It is not yet possible to define the optimum time for treating the asymptomatic patient with persistent post-molar trophoblast; it is likely to be between three and eight months post-evacuation and may be more closely defined by studies now in progress.

Treatment

Twenty-one patients with non-metastatic post-molar trophoblastic disease have been treated in our unit in the past forty months. Only 3 of them had children and only one had more than one child. In 15 patients the mole was the first pregnancy; their average age was 27 and the mean interval from evacuation was 4·8 months. All but one had arteriographic abnormalities and all excreted HCG. Three had undergone hysterectomy and in 2 of these the histological picture was chorion carcinoma.

In this almost childless group, hysterectomy was undesirable although it may be suitable for elderly multiparous patients. Systemic chemotherapy was also undesirable because of its toxicity and risk.

We have previously described a metabolite-antimetabolite method for treating these patients (Bagshawe & Wilde 1964), and further experience with it has confirmed our original impressions of its value. The tip of a small bore PTFE catheter introduced percutaneously via the femoral artery is positioned just above the aortic bifurcation. Methotrexate is infused through this by pump. Initially our regime gave 25–50 mg methotrexate daily, folinic acid intramuscularly 6–12 mg every twelve hours and 6-mercaptopurine 50–100 mg twice daily by mouth Subsequently the regime was modified by omission of the 6-mercaptopurine and by using a standard methotrexate infusion of 25 mg/day with folinic acid 6 mg every twelve hours. Recently we have used 5 mg methotrexate per day alone by infusion, without folinic acid but this has proved less satisfactory than the regimes with folinic acid. Each course of treatment is seven days in duration followed by five to eight days' rest before further treatment. Treatment is continued for 4–8 courses till gonadotrophin values have been in the normal range for four to six weeks and the total period of hospitalization two to four months.

All the patients in this group have responded fully to this treatment and relapse has not occurred. Toxicity has been negligible with only transient, moderate leucopenia. The usual effects of systemic chemotherapy such as thrombocytopenia, stomatitis, anorexia and hair loss are avoided.

One patient who started treatment during a bacteriæmia developed a femoral mycotic aneurysm which subsequently healed and another had an unexplained episode of acute glomerular

nephritis. Four patients have subsequently had successful normal pregnancies and 4 others are currently pregnant. It is emphasized that the regimes outlined here have not yet been shown to be suitable for other forms of trophoblastic neoplasia.

With the efficient application of assay methods now available and the form of treatment described here, death from post-molar chorion carcinoma could probably be eliminated. The technology exists, the clinical organization only is lacking.

It is suggested that carefully controlled chemotherapy of those post-molar patients who are demonstrably at great risk is preferable to the indiscriminate use of prophylactic chemotherapy for all patients with mole.

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Dr Magnus Haines (*Chelsea Hospital for Women, London*) said that fresh impetus and interest had been added to the study of disorders of the trophoblast since the topic was last discussed at a meeting of the Section (King 1956) when special emphasis had been placed on borderline cases amongst those with hydatidiform mole and chorion epithelioma. From that time the high incidence of these disorders in parts of the Orient had been generally accepted, from the experience of Dr Acosta Sison in the Philippines and more recently by Professor Tow in Singapore. Terminology had been difficult always to accept and both Dr Park and Professor Tow had shown that they were dissatisfied with current terminology, offering schemes of their own.

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Mr D J MacRae (*London*) demonstrated by slides of a case of chorion carcinoma which had occurred during pregnancy (MacRae 1951). The patient had reported with a history of one week's vaginal bleeding at the 33rd week of an otherwise normal pregnancy and examination had shown typical mulberry-like secondaries of chorion carcinoma at the vaginal outlet. A biopsy from one of these nodules had confirmed the diagnosis; the Aschheim-Zondek test had been positive in dilutions up to 1/1,000 and metastasis had also been demonstrated in the lung X-ray.

Cæsarean section had been performed securing a live, healthy baby of 5½ lb. The placenta had been bipartite and had had at its centre a tumour area, a yellow excrescence about the size and appearance of a groundnut, which on section showed malignant Langhans and syncytial cells growing from (or invading) normal placental villi. The myometrium of the apposed uterine surface had been occupied by malignant trophoblastic cells, which had also filled the sinuses. The patient had died on the seventh post-operative day and post-mortem had shown pronounced intravascular lung metastasis with limited parenchymal involvement, and secondaries in the vagina.

Mr MacRae asked where was the exact site of origin of malignancy in this case. Was it from normal villi in the placenta, or from villous elements which became detached and appeared deep in the myometrium and were not contained, or did it arise from metaplastic decidual cells which are said to be found on the fœtal side of the fibrinoid layer of Nitabuch (Park & Lees 1950)?

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Dr Wallace Park, in reply, said that Mr MacRae's case would appear to be one of those relatively rare instances where metastasizingly malignant chorion carcinoma developed within a small area of an otherwise normal placenta. The frequency of this occurrence was not known, the reason probably being the rarity with which 'ordinary' term placentas were closely scrutinized. It was quite uncommon for patients whose chorion carcinoma appeared to derive from a term pregnancy to develop manifestations of the carcinoma during the pregnancy itself. If this happened in every such case, the placenta would no doubt be as carefully examined as it was in that of Mr MacRae, and lesions of the same kind be not discarded but discovered.