Papers and Originals

Choriocarcinoma after Hydatidiform Mole. Studies Related to Effectiveness of Follow-up Practice after Hydatidiform Mole

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British Medical Journal, 1969, **3**, 733–737

Summary: Chemotherapy, in conjunction with other methods of treatment, was used in 100 patients with invasive hydatidiform mole or choriocarcinoma following mole. When treatment was instituted within two to six months of the antecedent mole serious drug resistance was not encountered, drug toxicity was slight, the duration of treatment was comparatively short, and sustained remissions were obtained in 57 out of 60 patients. When the start of chemotherapy was delayed beyond six months drug resistance occurred in many instances, toxicity was often severe, the duration of treatment was much longer, and sustained remissions were obtained in 22 out of 40 patients.

The practice of giving prophylactic chemotherapy to all patients with mole is not established as effective or safe. Differences in the social background to hydatidiform mole in different geographical areas may be such that conclusions based on evidence from one area are not necessarily applicable to another.

Careful follow-up after mole remains essential, though present methods often fail to ensure recognition of choriocarcinoma while it is still curable. Standard qualitative and quantitative methods for detecting the continued excretion of chorionic gonadotrophin, though useful, are sometimes too insensitive. It is suggested that to supplement local arrangements some form of centralized or regionalized follow-up service based on notification of patients with hydatidiform mole, and making use of radioimmunoassays for chorionic gonadotrophin, could reduce deaths attributable to late diagnosis.

Introduction

The incidence of hydatidiform mole in the United Kingdom is not known precisely, but probably some 500 to 1,000 cases occur each year. The risk of developing choriocarcinoma after hydatidiform mole is generally estimated at about 2–3% in western countries (Hamburger, 1944 ; Hertig and Sheldon, 1947 ; Delfs, 1959), a risk which is about a thousand times greater than after normal-term pregnancy (Schumann and Voegelin, 1937 ; Douglas, 1959 ; Yen and MacMahon, 1968). In addition, serious morbidity can result from invasive mole. Standard textbooks have long emphasized the need for the early diagnosis of these neoplastic sequelae to mole, and they generally recommend follow-up with uterine curettage for irregular bleeding, with pregnancy tests and chest radiographs, at frequent intervals for up to two years even in the absence of symptoms. These recommendations vary substantially (Table I), so clinicians may be uncertain about the best policy to follow.

TABLE I.—*Recommendations in Some Standard Texts for Use of Pregnancy Tests in the Follow-up of Patients after Hydatidiform Mole*

Textbook	Date of Publication	Interval Between Tests	Duration of Follow-up
A	1969	3–6 months	1½–2 years
B	1963	1 month	Some months
C	1963	2 weeks till negative, then 1 month for 6 months, then 3 months	1½ years +
D	1967	1 month at first, then 2 months	3 years
E	1965	Biological test, 3 months	2 years
F	1962	1 month	6 months

Since chemotherapy has greatly altered the prognosis of patients with gestational choriocarcinoma and has largely eliminated the need for hysterectomy for invasive mole it is appropriate to reconsider the question of following up these patients. It may be asked whether follow-up procedures achieve their objectives, whether they need to be improved, and even whether they are necessary at all.

Between 1959 and 1968 181 patients who had had hydatidiform moles were referred to this unit either for treatment of a trophoblastic neoplasm or for gonadotrophin studies to determine whether specific treatment was indicated.

Indications for Treatment

In 41 patients the extent of tumour spread in the abdomen, lungs, or central nervous system required immediate therapy. In others, where metastases were fewer or not in evidence, it was necessary to determine whether the tumour was likely to resolve spontaneously or whether it would continue to grow.

The rate of gonadotrophin excretion provided an index of trophoblastic activity which played a major part in the decision to treat many patients. Patients were judged to be excreting chorionic gonadotrophin (H.C.G.) if the rate of urinary excretion of gonadotrophin exceeded the normal range for pituitary gonadotrophins. The method used to estimate gonadotrophin excretion during 1959–60 was the mouse uterine weight assay (Klinefelter *et al.*, 1943), and during 1961–4 modifications of the haemagglutination inhibition assay (Wide and Gemzell, 1960) were used with kaolin-acetone or ultrafiltration extractions of the hormone. Since January 1965 radioimmunoassay (Wilde *et al.*, 1965, 1967) has been used on unextracted urine or plasma.

Pelvic arteriography (Borell *et al.*, 1955 ; Cockshott *et al.*, 1964 ; Brewis and Bagshawe, 1968) was also useful in some

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instances. The findings were consistent with invasive trophoblastic neoplasia in 66 out of 74 patients examined.

Patients were treated if, more than two months after the evacuation of a mole, the excretion rate of chorionic gonadotrophin was increasing progressively ; treatment was also given if a grossly raised excretion rate did not show a downward trend in a patient who had persisting uterine haemorrhage or pulmonary metastases, or if there was morphological evidence of choriocarcinoma. Patients who were still excreting chorionic gonadotrophin more than four months after evacuation were treated in the absence of other features unless their chorionic gonadotrophin excretion rates were falling progressively.

A few patients were treated by chemotherapy before two months had elapsed after evacuation of a mole, chiefly on account of uterine haemorrhage persisting after curettage ; but an exceptional patient had extensive dissemination within this early follow-up period. Hysterectomy was recommended for menopausal patients with persistently raised gonadotrophin excretion rates but no evidence of distant metastases ; where gonadotrophin values subsequently became normal and remained normal chemotherapy was not given.

Data

General

Of the 181 patients referred with trophoblastic activity after hydatidiform mole 100 were admitted for chemotherapy, and these 100 cases provide the data presented here. All the patients in the treatment series had been followed up elsewhere until referred to this unit because of sequelae. Five patients in whom a normal pregnancy or abortion intervened between evacuation of a mole and a diagnosis of choriocarcinoma were not included in the series. Otherwise, all those who had had mole were included regardless of the extent of their disease and notwithstanding previous chemotherapy elsewhere.

TABLE II.—*Parity* of Treated Patients*

Para-1	Para-2	Para-3	Para-4
43 (8)	27 (6)	13 (4)	17 (3)

* Total number of pregnancies including antecedent mole.
Figures in parentheses indicates number of deaths.

The patients' ages were 15 to 52 years, with a mean of 26·4 years. The mean number of living children per patient was 0·79 ; 47 patients were childless, 18 gave a history of one abortion, three of multiple abortions, and three of stillbirths. Their parity is summarized in Table II ; no relation was found between parity and mortality.

The methods used to evacuate the moles at the referring hospitals are summarized in Table III. Since there are no comparable data for unselected mole patients, the influence of the method of evacuation on the incidence of neoplastic sequelae cannot be assessed. Choriocarcinoma has followed all methods of evacuation including hysterectomy, though local complications from invasive mole after hysterectomy did not occur in this series.

TABLE III.—*Mode of Evacuation of Mole*

Spontaneous Expulsion and Curettage	Medical Induction and Curettage	Hysterectomy	Hysterotomy
59	21	3	17

Morphology

A morphological diagnosis of choriocarcinoma with the use of standard criteria (Park and Lees, 1950 ; Novak and Seah, 1954) was made on excised uteri, resected intestine and lung tissue, or necropsy material in 32 cases. Curettage material was consistent with choriocarcinoma in a further three instances. Invasive mole was present in two excised uteri and in curettings from four further patients. The remaining 59 had trophoblastic neoplasias of unknown type.

Apart from procedures carried out during the first week after evacuation of the mole, curettage had been performed on 168 occasions on the 100 patients before admission to this unit. Trophoblastic elements were present in a total of 114 instances, and on these a diagnosis of invasive mole was possible in five cases ; a conclusive diagnosis of choriocarcinoma could not be made on the curettings in any instance, but the findings were strongly suggestive of choriocarcinoma in nine patients, and this diagnosis was subsequently confirmed by hysterectomy or necropsy in six of these. The source of material providing the morphological evidence is summarized in Table IV.

TABLE IV.—*First Source of Material Providing Morphological Diagnoses in 100 Treated Cases*

	Total No.	Chorio-carcinoma	Invasive Mole	Not Diagnostic
Uterine curettings	168	9*	5†	154
Excised uterus:				
Before admission for chemotherapy	21	17	1	3
After start of chemotherapy	8	7	1	—
Resected gut	1	1		
Necropsy		7‡	—	

* Choriocarcinoma was confirmed by hysterectomy or necropsy in six of these.
† Invasive mole was later confirmed by hysterectomy in one case.
‡ Choriocarcinoma was present in all 18 cases brought to necropsy, but a morphological diagnosis had been established previously in 11 of these.

Chest Radiographs

A total of 135 chest radiographs were recorded during the follow-up of these 100 patients before referral for chemotherapy, making an average of one per 6·3 months of follow-up. On admission 64 patients had evidence of pulmonary metastases ; the incidence of metastases increased as the time between evacuation and referral increased (Table V).

TABLE V.—*Evidence of Pulmonary Metastases Present on Chest Radiographs on Admission for Chemotherapy*

	Interval between Evacuation of Mole and Admission for Chemotherapy in Weeks			
	< 13	13–25	26–51	52+
No. of cases	35	25	15	25
No. with metastases	17 (48%)	12 (48%)	13 (87%)	22 (88%)

Tests for Gonadotrophins

Pregnancy tests were recorded in 93 patients and the average number of tests per patient was 2·75, which is equivalent to one test per 3·1 months of follow-up. Fifteen different types of test were used, their minimum sensitivities ranging from about 1 to 20 i.u. H.C.G./ml. During the 10-year study period the average number of tests per patient has tended to increase slightly, and this has coincided with the shift from biological to immunological methods. The chorionic gonadotrophin excretion rates on admission are summarized in Table VI.

TABLE VI.—*Gonadotrophin Excretion Rates on Admission for Chemotherapy*

H.C.G. i.u./day	$< 10^3$	10^3–10^4	10^4–10^5	10^5–10^6	$> 10^6$
No. of cases*	3 (0)	22 (0)	47 (7)	18 (4)	9 (9)

* One patient died before samples were collected for assay.
The number of deaths in each group is indicated in parentheses.

Post-molar choriocarcinoma with an initial excretion rate higher than one million i.u. H.C.G./day always proved fatal. Since about one in three patients whose pregnancy tests are positive more than three months after evacuation have choriocarcinoma,

we have summarized the times which elapsed between the first of such positive tests and the time of admission for chemotherapy (Table VII). All patients were excreting chorionic gonadotrophin on admission and the excretion rate correlated closely with other criteria of viable tumour mass when these were present.

TABLE VII.—*Interval Between First Positive Pregnancy Test Obtained More than Three Months After Evacuation of Mole and Admission for Chemotherapy*

Interval between positive test and admission in weeks	< 10	10–19	20–29	30–39	40+
No. of cases (No. of fatal cases)	36 (6)	11 (0)	4 (3)	3 (2)	4 (4)

Pregnancy tests were not recorded for 7 patients.

Time from Evacuation of Mole to Chemotherapy

The average interval between evacuation of the antecedent mole and admission for chemotherapy was 8·5 months. When the patients are classified by the lapse of time between evacuation of the mole and the start of chemotherapy it is evident that mortality increases as this interval increases (Table VIII). In patients treated within six months the mortality rate was 5% and in those not treated until after 12 months it was 60%.

TABLE VIII.—*Interval Between Evacuation of Mole and Admission for Chemotherapy Related to Deaths*

Interval in Weeks:	< 13	13–25	26–51	52+
No. of patients	35	25	15	25
No. of cases with morphological evidence of choriocarcinoma	4	5	6	20
No. of deaths	2	1	3	15

All 60 patients treated within six months of evacuation responded to chemotherapy. Nevertheless, the uterine mass in one patient with invasive mole (Case 141) and in one with choriocarcinoma (Case 169) responded more slowly than the metastases, so hysterectomy was performed. Two deaths in this group were due to extensive dissemination of choriocarcinoma; one patient (Case 159) had recurrent tumour embolism to the pulmonary arteries and died two days after admission; a second patient (Case 240) died from multiple bleeding intestinal metastases five months after evacuation of her mole and six months after pulmonary metastases had first been identified. A third patient (Case 234), who was treated for early metastatic disease, died with jaundice from presumed serum hepatitis, a complication which two other patients survived.

All 40 patients who started treatment more than six months after evacuation showed an initial response to chemotherapy, but complete or partial resistance occurred later in 25 of them. Five had hysterectomy and four had lobectomy for resistant localized disease after starting chemotherapy. Seventeen deaths were associated with complete or partial drug resistance, and one patient, nursed in an open ward, died from infection during an influenza epidemic.

The difference in the overall mortality rates of those treated before and those treated later than six months after evacuation are significant ($P<0·01$). The difference in mortality is also significant ($P<0·01$) where the analysis is confined to those patients who had pulmonary metastases on admission, but it is not significant when confined to those for whom there was morphological evidence of choriocarcinoma.

Drug Regimen, Toxicity, Duration of Therapy

Patients treated during 1959–63 received methotrexate and mercaptopurine in combination (Bagshawe, 1963). A methotrexate-folinic acid regimen (Bagshawe, 1967, 1969) was introduced in 1963 for patients with early disease, but since 1965 it has been the initial treatment for all patients. This regimen largely avoids the stomatitis, alopecia, and nausea incurred from other cytotoxic regimens, and was the only treatment necessary in 43 out of 47 patients treated within six months of the antecedent mole and in 7 out of 18 whose treatment started later. Patients not responding to this non-toxic regimen were then treated with actinomycin D and other agents with the usual toxic effects.

The mean duration of therapy was 13·2 weeks for those treated within three months of evacuation of the mole and 38·4 weeks for those treated more than 12 months after evacuation (Fig. 1).

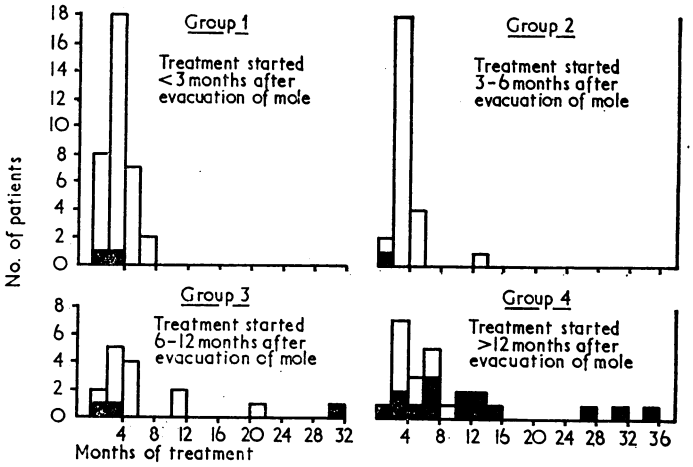

FIG. 1.—Relation between time at which chemotherapy was started and duration of chemotherapy. ■=Fatal cases.

The timing and nature of the follow-up procedures employed in patients who died after referral for chemotherapy are summarized in Fig. 2.

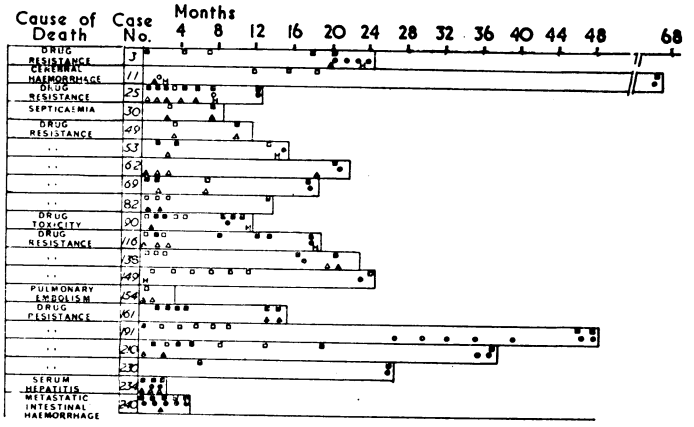

FIG. 2.—Investigations during interval between evacuation of mole and referral for chemotherapy in 20 patients who died during treatment. Pregnancy test: □=negative, ■=positive. Chest radiograph: ○=normal, ●=metastases present. Curettage: △=trophoblast absent, ▲=trophoblast present. H=Hysterectomy.

Remissions and Subsequent Pregnancies

A total of 21 patients have died and two are still under treatment. The remaining 77 have been in complete remissions for periods ranging from two months to 10 years, the mean duration of remission being 3·3 years. Two patients relapsed within two months of discharge after chemotherapy and were readmitted for further chemotherapy; they have since been in remission for seven years and one year respectively. Three patients who relapsed at intervals of two to six months after

discontinuing chemotherapy were readmitted but died during further chemotherapy and are included in the deaths in the series. Gonadotrophin follow-up studies have been maintained on 73 of the patients in remission.

Sixty-six patients in the series did not have hysterectomy and 24 of these have subsequently had 27 normal-term deliveries; three have aborted and one had a premature stillbirth. One child died from spina bifida; no other congenital abnormalities have been reported to us.

Discussion

Women who have hydatidiform moles form a comparatively small and well-defined population in which for a limited period of time there is a high risk of a rapidly growing cancer. Since the ensuing cancer is at least potentially curable and since techniques for its detection at an early stage are available, we have to regard fatalities from this tumour as a failure to exploit available resources. On the other hand, the techniques for early diagnosis do not readily discriminate between potentially fatal proliferations and those which regress spontaneously.

The natural history of trophoblastic cells remaining in the uterus and elsewhere after evacuation of a hydatidiform mole is complex, so that if we base clinical policies on oversimplifications of the problem they inevitably will not fit certain situations. The trophoblastic fragments which progress to a true malignant state are generally inaccessible to the curette and to histological examination, so that knowledge of their natural history depends heavily on gonadotrophin studies and on radiological examinations. Our studies with gonadotrophin assays sensitive enough to detect normal levels of luteinizing hormone are broadly consistent with those of previous workers (Hamburger, 1944; Delfs, 1959; Brewer *et al.*, 1968) which indicated that in about 80% of cases trophoblastic activity is no longer detectable by 60 days after evacuation and in 90–95% cases by the 250th day. Present evidence is that sequelae have not occurred in patients whose gonadotrophin excretion rates have been repeatedly within the normal range of pituitary activity. The longer trophoblastic activity has been detectable the greater has been the incidence of choriocarcinoma, but choriocarcinoma may cause death within 60 days of evacuation of a mole, so there is no natural point for a temporal demarcation between regressing and potentially lethal proliferations.

Factors in Failure of Follow-up Methods

It is apparent from this series that strenuous efforts have been made by clinicians to achieve good follow-up of their patients with mole, but that this is difficult to achieve. Diagnostic delays have resulted from a variety of factors such as patients' failure to keep appointments. They have also resulted from technical failures with pregnancy tests, from the use of particularly insensitive pregnancy tests, from the inadequate sensitivity for this purpose of even the most sensitive pregnancy tests, from the failure of positive reports to reach the attention of the clinician responsible, and from failure to interpret both positive pregnancy tests and radiological evidence of pulmonary metastases as evidence of a potentially fatal process. Curettage resulted in prompt action on the few occasions when it provided diagnostic evidence, but the more common negative results were often followed by prolonged diagnostic inactivity. Chest films were taken somewhat infrequently even in patients with pulmonary symptoms. A few patients said that no arrangements were made for clinical examination or follow-up tests after their moles had been evacuated, and the records from the referring hospital did not always refute the possibility that follow-up had been overlooked. The evidence from this series therefore suggests that follow-up practice tends to fall short of that generally thought necessary.

Where recommended procedures were regularly employed delays in diagnosis were fewer but they were not eliminated. For instance, one patient who had undergone hysterectomy a week after evacuation had had six negative pregnancy tests during the ensuing 12 months, but a year after her last test she was found to have massive pulmonary metastases, which ultimately proved fatal. A major factor in the efficiency of follow-up is therefore the dependability of pregnancy tests. The most sentitive pregnancy tests are only just sensitive enough to detect concentrations about 10 times as high as peak normal values of luteinizing hormone. Similarly, quantitative assays based on standard pregnancy tests are no more sensitive. These tests are therefore inadequate for following up patients with mole.

The evidence from the present series indicates that the outcome of treatment for post-molar trophoblastic tumours is good when chemotherapy is started within two to six months of their evacuation. The death rate in these patients was 5% and the failures were not attributable to drug resistance or drug toxicity. When chemotherapy started more than six months after evacuation of a mole the death rate was 45%, and with two exceptions the deaths were associated with drug resistance. Delayed recognition incurred prolonged treatment and increased toxicity as well as greatly reduced prospects of recovery.

The arbitrary division of patients into those treated within six months of evacuation of the mole and those treated later does not provide strictly comparable groups. It is possible that some tumours might have undergone spontaneous regression if not treated, and this would be more likely in the cases treated early than in those treated later. It is also likely that there were more invasive moles in the early than in the late groups, and these have a more favourable prognosis. Again, choriocarcinomas giving rise to symptoms early, or detected by other means in the early months after evacuation, might differ from those detected only after a longer interval. The influence of these factors cannot be adequately assessed on the firm ground of morphological evidence, since successful therapy militates against obtaining that evidence; but the difference in overall mortality between those treated within six months of evacuation and those treated later, and the difference in the incidence of drug resistance, provide a strong prima facie case for concluding that early diagnosis and treatment are favourable.

Prophylactic Chemotherapy; Hysterectomy

It has been recognized for a few years that trophoblastic proliferations which occur soon after evacuation of mole respond better to chemotherapy than late ones, that follow-up often fails, and that pregnancy tests are often inadequate. It has therefore been advocated, principally by workers in geographical areas where mole is common, and where follow-up is more difficult than in Europe, that all patients with hydatidiform mole should be treated with prophylactic chemotherapy or hysterectomy. If giving chemotherapy at the time of evacuation were safe, and effective, it would avoid the problems of follow-up and late treatment.

Kaku (1966) concluded from his series that prophylactic chemotherapy had not resulted in a significant reduction of neoplastic sequelae. Manahan *et al.* (1967) reported that, contrary to an earlier favourable report, prophylactic methotrexate had been followed in four instances by fatal choriocarcinoma. These authors felt that for it to be effective, repeated courses would be necessary and toxicity incurred. Koga and Maeda (1968) treated 107 patients with *methotrexate in total* dosages of 70–340 mg. and found two invasive moles but no choriocarcinomas during follow-up for six months or more. There were, however, some cases of choriocarcinoma in a group which received prophylactic methotrexate only three weeks after evacuation. There were no known cases of choriocarcinoma among the 200 mole patients reported in the series of Hunt *et al.* (1953), Smalbraak (1957), and Marquez-Monter *et al.*

(1963), none of whom received chemotherapy, so that the effectiveness of prophylactic chemotherapy can be demonstrated only in much larger series than those so far reported.

"Prophylactic chemotherapy" and "chemotherapeutic umbrellas" may be useful in antibiotic therapy, but it seems important that these evocative concepts should not be transferred to antimitotic therapy without both effectiveness and safety being established. In our experience the hazards of methotrexate and actinomycin D therapy are greatly increased in the postoperative period and in the presence of infection. Such effects are rarely taken into account in recommended therapeutic schedules and we have noted that one current textbook recommends a dosage of 20 mg. of methotrexate daily for up to seven days, a regimen which we suspect would be lethal to a high proportion of healthy women. Deaths from prophylactic chemotherapy have not, so far as we know, been published to date, but four such instances have been described to us in personal communications during the past year. We have also been informed of deaths after hysterectomy of women receiving as little as 60 mg. of methotrexate in three days. Nor can the problem be resolved by using a low-dosage regimen, since this may favour the development of drug resistance. Even if prophylactic chemotherapy were effective it would seem undesirable to expose 25 to 50 women to cytotoxic agents for every one at risk to a serious neoplasm, and in its present form it could result in substantially more deaths than choriocarcinoma.

The present series does not provide a sound basis for advocating or disputing the case for hysterectomy as effective prophylaxis against the neoplastic sequelae of mole. In the U.K. moles are not often removed by hysterectomy, though it may be noted that there are three patients in the present series who developed metastatic disease despite initial hysterectomy. It is also relevant that advocacy of prophylactic hysterectomy based on series from Hong Kong and Singapore (Chun *et al.*, 1964 ; Fox and Tow, 1966) related to patients with an average parity of 3·6 and 4·0 respectively, compared with an average parity in the present series of less than one.

If prophylactic treatment is neither highly effective nor reasonably safe, then systematic follow-up and case selection for specific therapy is essential. The object of follow-up examinations is clearly to identify as soon as possible those who need treatment and to spare those who do not.

New Techniques and Follow-up Problem

Brewer *et al.* (1968) advocated chemotherapy for all those patients who can be shown by a sensitive assay method to be excreting chorionic gonadotrophin when the uterine cavity is empty, 60 days after expulsion of the mole. We agree with these authors that this policy is much to be preferred to treating all mole patients with chemotherapy, and it has the virtue of reasonable simplicity ; but on their data more than 20% of mole patients would be treated, a figure which is still almost 10 times the estimated incidence of fatal choriocarcinoma after mole. Clearly, the apparent effectiveness of treatment in a series is enhanced the greater the number of early post-molar cases included in it, simply because these have a higher rate of natural regression.

Experience with radioimmunoassay estimations of gonadotrophin excretion suggests that the general availability of this technique, coupled with the indications for treatment outlined in this paper, would permit case selection for specific therapy to be limited to about 7% or less of mole patients without risking diagnostic delays which might result in resistant disease.

Radioimmunoassay for chorionic gonadotrophin is a comparatively complex technique (Bagshawe *et al.*, 1966 ; Wilde *et al.*, 1967) but one which is convenient for large-scale use. Reliable estimations can be made on 10-ml. aliquots of 24-hour urine collections with merthiolate (100 mg.) as preservative. A case can therefore be made for having some form of centralized follow-up service for patients after the evacuation of moles. By making hydatidiform mole a "notifiable disease," or by some other registration scheme, it could be arranged for patients to be sent instructions and requisites for urine collections from a central laboratory. The patients would post the specimens to the laboratory, which would in turn send the assay result to the referring clinician and inform the patient when to send in the next specimen. Such a service would aim not to replace follow-up arrangements made locally but to provide the clinician responsible for the patient with supplementary information.

A full radioimmunoassay service could be provided for all mole patients at a small fraction of the cost of admission to hospital for prophylactic chemotherapy.

We wish to thank the numerous clinicians who have referred patients and who have generously made records available to us. We also wish to thank Dr. A. G. J. Rushworth and Dr. P. A. Walden for help with case histories, and Sister M. Willows and her staff and Mrs. Constance Goodridge for their invaluable assistance.

Part of the studies described here were supported by grants from the Medical Research Council and the British Empire Cancer Campaign for Research.

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