Trophoblastic tumours

The histopathology of trophoblastic tumours

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Two important advances in the last 40 years have had a profound effect on the prognosis of patients with trophoblastic tumours. In the first place the application of gonadotrophin assay, initially by biological methods and then by the more accurate radioimmunological methods, to the diagnostic problems of patients with trophoblastic disease has made their management considerably easier. Secondly the discovery that choriocarcinoma, previously among the most rapidly fatal of all tumours, was amenable to treatment with cytotoxic agents has revolutionized therapy, with a reduction in the crude death rate from over 85% to less than 20%.

It has been increasingly suggested that with the growing use of diagnostic aids such as gonadotrophin assay, arteriography and radiography, the usefulness of histological examination has diminished. In some cases this is true; for instance, in the follow up of a patient with hydatidiform mole, when, in the face of a persistently raised gonadotrophin excretion, it may be inadvisable to delay treatment by waiting for histological confirmation of the diagnosis. Nevertheless, curettage is still widely used as the initial diagnostic procedure in the investigation of uterine bleeding, and it is in this situation that the histopathologist will be confronted by the problem of the difficult trophoblastic curetting. Furthermore, the final diagnosis of malignancy, with trophoblastic as with any other tumour, should still ideally be made on histological grounds. Failure to recognize this has resulted in exaggerated claims for cure rates, by including in a malignant category, without histological proof, cases which have pursued an apparently benign course.

A major drawback in investigating these tumours fully has been the difficulty in collecting together enough cases for a detailed study. For instance, in Britain most clinicians and pathologists are unlikely to see more than two or three cases of choriocarcinoma in their professional lives. The author was particularly fortunate in being associated with Dr Kenneth Bagshawe's Unit at Charing Cross Hospital, London, for a number of years, with

access to the pathological material and case records of over 200 patients with trophoblastic disease. It is on this material that the current review of the pathological aspects of trophoblastic disease is based.

Classification of Trophoblastic Disease

Although there are those who maintain that in classifying diseases we conceal more than we clarify, most accept that some form of classification is necessary. This is particularly true in the case of neoplasms, where an ideal classification carries an implication of prognosis, and the choice of therapy may depend on the tumour type. The basis of modern classifications of trophoblastic neoplasia was provided by Ewing (1910) who thought that more importance could be attached to histological appearances in relation to the degree of malignancy than had previously been claimed. He grouped all trophoblastic tumours under the general term 'chorioma' and recognized the following subdivisions: (1) hydatid mole, (2) chorioadenoma destruens, (3) choriocarcinoma, (4a) syncytial endometritis, (4b) syncytioma.

At first sight it may seem incongruous to include hydatidiform mole in a classification of trophoblastic tumours, since a mole is essentially a particular type of abortion, and in the great majority of cases there are no neoplastic sequelae. Theoretical considerations of the malignant potential of molar trophoblastic hyperplasia have received much attention (Hertig and Sheldon, 1947; Schopper and Pliess, 1949; Park, 1971), but the important practical point is that in at least 50% of cases choriocarcinoma is preceded by a hydatidiform mole. This undoubted close association makes it eminently sensible to place the two lesions together in the same classification.

The precise status of Ewing's second group of chorioma, the chorioadenoma destruens, has also been questioned. In the first place the term itself, derived from the idea that the chorionic villus is a gland, and the lesion relatively benign, has not found

universal favour. This has been more fully discussed by Park (1971) who argues persuasively in favour of 'invasive hydatidiform mole' as an alternative. A more important point is the question of its neoplastic potential. Tow (1966) considered that invasive mole should be renamed 'villous choriocarcinoma' and that choriocarcinoma be called 'avillous choriocarcinoma'. He argued that the villous form was merely an early stage of the avillous form and that, in his practice at least, both lesions received essentially the same type of treatment. This, of course, is not the case in Europe and the United States, and Tow's classification has not been well received (Bagshawe, 1969; Park, 1971). This point will be referred to again, but from the practical point of view there certainly seem to be good grounds for retaining the distinction between the two lesions.

INTERNATIONAL UNION AGAINST CANCER
CLASSIFICATION OF TROPHOBLASTIC
NEOPLASIA A = GESTATIONAL; B = NON-
GESTATIONAL
Park (1971) has recently made a plea for the more general adoption of the classification, proposed by a committee of the International Union against Cancer (1967), which has the advantage of both clinical and pathological categories, as shown below:

Clinical Diagnosis	Morphological Diagnosis
1 Non-metastatic	1 Hydatidiform mole
2 Metastatic	a Non-invasive
a Local (pelvic)	b Invasive
b Extrapelvic	2 Choriocarcinoma
	3 Uncertain

A disadvantage of this classification is the 'uncertain' category which will probably be the largest group in the present era when so many patients receive chemotherapy before a tissue diagnosis is established. Elston and Bagshawe have used the terms 'persistent trophoblastic proliferation' and 'persistent trophoblastic disease' in an attempt to be more precise (Elston, 1970; Elston and Bagshawe, 1972a and b), and the latter is perhaps less cumbersome. The classification by the International Union against Cancer deliberately excludes 'syncytioma' or 'syncytial endometritis' from the spectrum of trophoblastic neoplasia, and, although Ewing (1910) and Hertig and Sheldon (1947) considered these lesions to be choriocarcinomas of limited malignancy, there is no convincing evidence for this view, and they are best regarded as an exaggerated form of placental site reaction. Nevertheless, placental site reaction, and the exaggerated form in particular, may cause significant diagnostic difficulty, both clinically and pathologically, and for this reason, and for the sake

of completeness, the following modification of the morphological classification by the International Union against Cancer is offered:

- MODIFIED PATHOLOGICAL CLASSIFICATION OF
GESTATIONAL TROPHOBLASTIC DISEASE
- 1 Placental site reaction
 - a Normal
 - b Exaggerated
 - 2 Hydatidiform mole
 - a Non-invasive
 - b Invasive
 - 3 Persistent trophoblastic disease
 - 4 Choriocarcinoma.

Hydatidiform Mole

A hydatidiform mole is an abnormal product of gestation, usually associated with a blighted ovum. The morphological features of the 'classical' mole are so well described in the standard textbooks of pathology and gynaecology that they need little discussion here. It is recognized grossly by its

Fig 1 Hydatidiform mole, with marked stromal hydropic change, absent stromal blood vessels and slight trophoblastic hyperplasia. H & E $\times$ 50.

typical 'bunch of grapes' appearance and the microscopical features (fig 1) are: (a) hydropic swelling of the villous stroma giving rise to vesicles (these varying from 0.1 to 3 cm in diameter); (b) absence, or virtual absence, of fetal stromal blood vessels; (c) a variable degree of trophoblastic hyperplasia.

HYDROPIC CHANGE IN THE PLACENTA

Although no difficulty should be experienced in distinguishing a typical hydatidiform mole from 'normal' placental tissue derived from a spontaneous or therapeutic abortion (fig 2), a 'hydropic abortion' may give rise to diagnostic problems. In the latter there are no obvious gross abnormalities (or at most an occasional vesicle is seen), but microscopically a variable number of hydropic chorionic villi is present. Such hydropic change in placental tissue has long been recognized as a relatively common finding in abortuses (Meyer, 1919) and has been investigated in detail by Hertig and Edmonds (1940) and by Nilsson (1957). The practical implications of the problem are quite clear (Park, 1971). If the process that causes the hydropic abortion is the same biologically as that which causes the classical hydatidiform mole, then the lesion is important, and the same close follow up which is given to patients with the classical lesion should also be applied to those with a hydropic abortion. If the process is not the same then the lesion is insignificant. Unless this question can be answered satisfactorily there will always be the danger of inadequate follow up of patients who are at risk of developing postmolar choriocarcinoma or over supervision of patients who have no likelihood of developing choriocarcinoma. From their comprehensive investigation into the genesis of hydatidiform mole Hertig and Edmonds (1940) had no doubt that focal hydropic change in abortuses was part of a spectrum of changes leading up to the classical hydatidiform mole. They found a high incidence of 'blighted ova' in products of spontaneous abortion, with hydropic change in 67% of those with pathological ova and only 12% of those with non-pathological ova. These findings have been substantially confirmed by Nilsson (1957), who also found hydropic change to be more frequent with abnormal ova. Hertig and Edmonds concluded that the primary abnormality was early death of the fetus with failure of development of the chorionic blood vessels, leading to accumulation of fluid in the stroma in the presence of continuing secretory activity by the trophoblast. They introduced the concept of the 'transitional hydatidiform mole' in which the embryo is either abnormal or absent, grossly the placental tissue shows only occasional vesicles, and yet microscopically there is widespread hydatidiform degeneration of the villi, with focal

Fig 2 Normal chorionic villi from a therapeutic abortion at seven weeks' gestation. Note the regular two-layered trophoblastic layer, and the nucleated fetal red cells in stromal blood vessels. Haematoxylin and eosin $\times 175$.

trophoblastic hyperplasia.

Park, who has long maintained his opposition to the concept that molar change is caused by early fetal death (Park, 1959, 1967, 1971), feels that too much emphasis has been placed on the hydropic degeneration and too little attention paid to the trophoblastic hyperplasia. He has proposed that the trophoblastic proliferation may be the primary lesion, with oversecretion by the abnormal trophoblast leading to villous hydrops and thus vascular obliteration and blighting of the embryo. Whichever theory is correct, if we return to the practical implications of the problem, it is certainly true that the significant feature shared by hydatidiform mole and choriocarcinoma is the epithelial (trophoblastic) abnormality. Park (1971) has therefore suggested that in these lesions the state of the epithelium should be given priority as follows:

- 1 Where hydrops of the villus, whether it amounts

Fig 3

Fig 3 Chorionic villi from a spontaneous abortion at nine weeks' gestation. There is hydropic change in the stroma with absent blood vessels, and the trophoblast is two-layered but attenuated. H & E $\times 175$.

Fig 4

Fig 4 Same case as that shown in figure 2. In this field there is marked trophoblastic hyperplasia. H & E $\times 175$.

to frank liquefaction of the stroma or not, is accompanied by hyperplasia of the trophoblast, the conceptus should be designated 'hydatidiform mole'.

2 Where villi with this type of stromal change have no associated trophoblastic hyperplasia, the conceptus should be designated 'hydropic abortion'.

3 No distinction should be drawn between villous hydrops visible macroscopically as distinct vesicles and villous hydrops visible only macroscopically.

This is an arbitrary procedure, but on a practical basis it seems to work. Essentially similar criteria have been used for several years in our department at the City Hospital, Nottingham, in the examination of many thousands of gestational products. So far, no case of choriocarcinoma has occurred in a patient whose original products of conception were described as a simple hydropic abortion, and this is in accord with Park's experience (1971).

Although the criteria outlined above are relatively

straightforward, difficulty in assessing trophoblastic proliferation may be experienced in some cases. Figure 3 shows a representative area from a hydropic abortus. No embryo could be identified, and although there was widespread hydropic change, most of the trophoblast was regular and two-layered. However, there was quite definite trophoblastic hyperplasia in other areas (fig 4) and although the overall appearances were not those of molar change, the patient was followed up. In the event urinary gonadotrophin levels rapidly became normal, and there were no sequelae. It is in the occasional borderline case such as this that our knowledge is lacking, and if there is any degree of uncertainty follow up with gonadotrophin assay is recommended.

PROGNOSIS OF HYDATIDIFORM MOLE: THE ROLE OF HISTOLOGICAL GRADING

In the United Kingdom choriocarcinoma is preceded

by a hydatidiform mole in about 50% of cases. Conversely, less than 5% of patients who abort a hydatidiform mole later develop choriocarcinoma, and fewer than 10% require treatment to eliminate trophoblastic disease. The clinical problem is then that, whilst the great majority of patients who abort a hydatidiform mole have no further trouble, a smaller proportion will inevitably require cytotoxic therapy. Management would be considerably simplified if this potentially malignant group could be identified at the time of molar abortion. The possibility that the malignant potential of the trophoblast of a hydatidiform mole could be predicted from its original histological appearances was first suggested by Hertig (1937). In a later study (Hertig and Sheldon, 1947), six histological grades were identified, relating increasing trophoblastic hyperplasia and anaplasia to increasing malignant behaviour. Hertig and Mansell (1956) subsequently modified the classification to include only three grades. Hunt *et al* (1953), using the criteria of Hertig and Sheldon, found that although a histological classification could be made the results were not definitive enough to determine treatment. This view was also held by Smalbraak (1957), Coppleson (1958), Logan and Motylloff (1958) and by Tow and Yung (1967), but Schiffer *et al* (1960) and Douglas (1962) considered histological grading to be of prognostic value. Park (1959) assessed the risk of malignant change as ranging from 1% with minimal trophoblastic hyperplasia to 10% with marked hyperplasia, and later stated that 'the correlation between degree of overgrowth and likely clinical behaviour is certainly low, but not entirely lacking' (Park, 1971).

As part of a wider study of the pathology of trophoblastic disease (Elston, 1970) an attempt was made to resolve these differences, particularly as the follow up given to many patients can still be influenced by the histological report on the original hydatidiform mole. The results have been published more fully elsewhere (Elston and Bagshawe, 1972a), but a summary of the findings is relevant here. The study was based on histological material obtained from 70 patients treated at Charing Cross (Fulham) Hospital. The criteria of Hertig and Mansell were used, giving three grades of trophoblastic hyperplasia and anaplasia. This was a selected group of patients in which there was a bias towards those who developed choriocarcinoma. Whereas only about 2% of hydatidiform moles are followed by choriocarcinoma in European populations (Kolstad and Hognestad, 1965; Ringertz, 1970) this occurred in at least 21% in our study. If the Hertig thesis were valid two trends would have been expected, an excess of grade 3 moles in the series as a whole, and

an excess of choriocarcinomas arising in those patients who did have grade 3 moles. In fact, the incidence of grade 3 moles (18.5%) was less than would have been expected by chance alone (33.3%). Further, the number of patients in each grade who subsequently developed choriocarcinoma was approximately that which would have been expected if the histological appearances had no influence on subsequent malignancy (grade 1, observed eight, expected 6.6; grade 2, observed four, expected 5.5; grade 3, observed three, expected 2.8). It was concluded that there was no value in attempting to assess potential malignant behaviour from the histological appearances of a hydatidiform mole. Indeed it may be an extremely dangerous practice, with delay in the diagnosis of choriocarcinoma arising from grade 1 moles or overdiagnosis of malignancy in grade 3 moles.

It seems clear that, in the absence of strong alternative evidence, attempts to identify the potentially malignant group of hydatidiform moles from their histological appearances should be abandoned. Indeed, this type of analysis has been superseded by the development of the relatively cheap and highly accurate radioimmunoassay method for estimating gonadotrophin levels. There is no substitute for careful follow up of all patients with hydatidiform mole (Bagshawe, 1969), and this should be based on regular clinical examination, with urinary gonadotrophin assay, radiographs of the chest, and, when indicated, histological examination of uterine curettings. The microscopical appearances of the original hydatidiform mole should not influence future treatment, and the terms 'malignant mole' and 'choriocarcinoma *in situ*' should never be used.

INVASIVE HYDATIDIFORM MOLE

An invasive mole may be defined as a hydatidiform mole in which molar villi have penetrated the myometrium or its blood vessels. Apart from villous penetration of the uterus itself, an invasive mole may also produce villous or trophoblastic 'metastases'.

Ewing (1910) was the first to separate invasive mole from choriocarcinoma on clinicopathological grounds, because the average 'chorioadenoma' offered a hopeful prognosis, while choriocarcinoma did not. Since then there have been numerous reviews of invasive mole (Novak and Seah, 1954b; Hertig and Mansell, 1956; Greene, 1959; Acosta-Sison, 1960; Park, 1971), with general agreement that the entity is a useful one. However, Tow (1966) and Brewer (1967) have questioned this, considering that the separation of the two lesions is artificial, the characteristics of the trophoblast being of more

importance than the presence or absence of villi. It has further been stated that since a patient with either lesion is going to receive essentially the same treatment the precise histological diagnosis is not important. This is not necessarily true, and patients who have undergone surgical treatment for choriocarcinoma usually need follow-up cytotoxic therapy, which is rarely necessary in the case of invasive mole. Ewing's (1910) observation still holds good, and Park (1971) has suggested that trophoblast of the locally invasive lesion, which is capable of forming villi, is biologically different from that of the metastasizing malignant type that we recognize as choriocarcinoma. The question of so-called metastases in invasive mole is discussed later, but in view of the undoubtedly less aggressive behaviour of this condition, and the presence of villi as a distinctive marker, there are excellent reasons for retaining it as an entity separate from choriocarcinoma.

There are no typical macroscopic features in invasive mole, as there are with choriocarcinoma. The gross appearance depends on the extent of invasion; the uterus may show little abnormality apart from a small haemorrhagic focus, or there may be a large cavitating haemorrhagic lesion extending deeply into the muscle. More rarely the serosal surface of the uterus is breached. Occasionally, the original hydatidiform mole is still retained within the uterine cavity.

Microscopical examination of invasive moles must, by definition, reveal chorionic villi within the myometrium. The trophoblast exhibits no specific features; although in the majority of cases there is moderate or marked hyperplasia, in a significant minority little trophoblastic proliferation is seen. Three degrees of invasion can be recognized.

1 In a small proportion of cases invasion is limited and although molar villi and hyperplastic tropho-

Fig 5

Fig 5 Hydatidiform mole with limited invasion. Molar chorionic villi are attached to degenerate decidua. H & E $\times 100$.

Fig 6

Fig 6 Same case as figure 5. In this field hyperplastic trophoblast at the top is attached directly to myometrial fibres at the bottom, with conspicuous giant trophoblastic cells in the centre. H & E $\times 200$.

Fig 7 Invasive hydatidiform mole, with molar villi lying within a dilated venous sinus deep in the myometrium. H & E $\times 40$.

blast are attached directly to subendometrial myometrium (figs 5 and 6), without intervening decidua, there is no deeper invasion of the uterus by villi or trophoblast.

2 In the majority of cases there is deep penetration by molar villi into, but not through, the myometrium (fig 7). This penetration appears to take place almost invariably within dilated venous sinuses. The molar villi vary considerably in size, and occasionally are inconspicuous, so that the examination of any uterus containing a proliferating trophoblastic lesion requires a careful search for villi to avoid an erroneous diagnosis of choriocarcinoma. Placental site reaction is variable, and trophoblastic emboli in myometrial vessels are not infrequently seen.

3 In a minority of cases molar villi have penetrated through the full thickness of the myometrium, with perforation of the uterus or penetration into the broad ligament.

Hertig (1950) regarded these three degrees of invasion as the placenta accreta, increta and percreta

of the molar placenta. He found (Hertig and Mansell, 1956) that the sooner a hysterectomy was performed after diagnosis of a mole the more likely was evidence of local invasion to be found, and it is probable that all moles are at least minimally invasive (Gore and Hertig, 1967). Wilson *et al* (1961) and Gore and Hertig (1967) have commented on the difficulty of establishing the diagnosis in invasive mole, partly because of the scarcity of well formed villi in pathological material. It is possible that villi will only be present in a minority of the blocks taken, and for this reason multiple blocks should be examined.

The highest recorded mortality in invasive mole is 20% (Prawirohardjo *et al*, 1957) in the Far East, while in the United States, Greene (1959) found a mortality of 14% in a study of 42 selected cases. In many of the reported cases the precise cause of death is uncertain, because adequate necropsy records are lacking, but the impression gained is that the mortality is related more to local complications such as haemorrhage or uterine perforation than to progressive metastatic disease. There were no deaths in the 10 patients from the Charing Cross series studied personally (Elston, 1970), and none have occurred subsequently in a much larger group of patients (Bagshawe, 1976). These results serve to emphasize the essentially limited aggressiveness of invasive mole.

'METASTASES' IN HYDATIDIFORM MOLE

A hydatidiform mole should be placed in the 'invasive' category not only when there is clear evidence of myometrial penetration but also in the presence of 'metastases'. As Park has pointed out (Park, 1971), the term 'metastasis' need not be synonymous with 'malignant neoplastic metastasis', and deportation of 'benign trophoblast' to the lungs in eclamptic and other maternal deaths is well documented (Schmorl, 1893; Veit, 1901; Bardawil and Toy, 1959). There have been numerous reports of metastasis in molar pregnancies, with frequencies of 24% (Greene, 1959), 27% (Acosta-Sison, 1960) and 40% (Wilson *et al*, 1961). Tow (1966), in a review of the world literature, found an overall figure of 35%, and this is in close accord with the estimated 36% in the selected series of hydatidiform moles examined by Elston (1970). The majority of reports refer to lung metastases confirmed only by radiographs of the chest, but several authors have recorded cases with histological proof of the molar or trophoblastic nature of the lesions (Delfs, 1957; Reed *et al*, 1959; Jacobson and Enzer, 1959; Wilson *et al*, 1961; Ring, 1972). Villous metastases have been recorded only rarely outside the pelvis and lungs (paraspinal connective tissue, Delfs, 1957;

spinal cord, Hsu *et al*, 1962; and brain, Ishizuka, 1967). From a clinical point of view the importance of metastases in molar trophoblastic disease is whether or not their presence implies that 'progressive' malignant change has developed. Biopsy may show unequivocal choriocarcinoma, in which case the diagnosis is certain, or it may show simple deported trophoblast or villi. Several authors have stressed the essentially non-malignant nature of such deported trophoblast or villi (Thiele and Alvarez, 1962; Hsu *et al*, 1962; Ring, 1972) as compared with choriocarcinoma.

In the patients treated at Charing Cross Hospital we did not have the opportunity to obtain biopsies from lung lesions except in cases of confirmed choriocarcinoma. Lung 'metastases' were therefore assumed from radiographic evidence, and the cases designated as 'persistent trophoblastic disease, metastatic'. There were no deaths in these patients, although some needed treatment with cytotoxic agents in order to obtain regression of the lung nodules. We did, however, have the opportunity to study the histological aspects of a number of vaginal 'metastases' which developed in patients with hydatidiform mole. It is appropriate to discuss the findings here, because, from a study of the early management of these patients, it is apparent that the presence of a vaginal nodule is frequently taken to indicate an unfavourable prognosis. Vaginal nodules developed in seven out of 72 patients with hydatidiform mole. In three cases the vaginal nodule was the presenting lesion, in two cases the nodule became apparent at the time of diagnosis, and in the other two cases the vaginal metastasis developed after abortion of the mole. In none of the patients was there any clinical or radiological evidence of other metastases. Choriocarcinoma did not develop in any of the patients: three required no therapy at all; one, who had a hysterectomy (performed mainly because a diagnosis of choriocarcinoma had been made from the presenting vaginal nodule), required no subsequent treatment; three were given up to four months' treatment with chemotherapeutic agents, an average course for postmolar trophoblastic disease.

In five of the seven patients a biopsy was taken, and the findings were as follows:

Case 65

Two months after her last period this patient developed vaginal bleeding, and was found to have an enlarged uterus with several vaginal nodules. Histological sections from one of the nodules were reported as choriocarcinoma, and she was transferred to Charing Cross Hospital. Treatment with intraarterial methotrexate was started, but the

Fig 8 Molar villus with adjacent vaginal mucosa, obtained at biopsy of a vaginal nodule in a patient with hydatidiform mole. H & E $\times 50$.

uterine bleeding continued, and one month after the vaginal biopsy a hydatidiform mole was expelled spontaneously. The patient is well 11 years later.

The original diagnosis of choriocarcinoma was incorrect, since the biopsy specimen contained hydropic chorionic villi (fig 8). Had this been made apparent at the time the delay in the diagnosis of the *in-situ* hydatidiform mole might not have occurred.

Case 67

During her first pregnancy this patient developed bleeding from a nodule in the vagina. Sections from the biopsy showed a deposit of molar villi in the vaginal mucosa. Two weeks later abdominal hysterotomy revealed a typical hydatidiform mole. As a pregnancy test was still positive one month later she was referred to Charing Cross Hospital for assessment. No treatment was given and the gonadotrophin excretion fell to normal over the next three months. The patient is well 10 years later.

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Fig 9

Fig 9 Vaginal nodule in hydatidiform mole. A small cavity at the bottom right is surrounded by inflammatory cells and an occasional large trophoblastic cell. H & E $\times 80$

Fig 10

Fig 10 Higher magnification of nodule shown in figure 9. There are scanty pyknotic trophoblastic cells, but no organized pattern is seen, and there are no chorionic villi. H & E $\times 160$.

Case 76

This patient was found to have a vaginal nodule following an 18-week period of amenorrhoea. Sections from the biopsy were reported as 'very strongly suspicious of choriocarcinoma'. Because of this she was referred to Charing Cross Hospital and hysterectomy was performed. Examination of the excised uterus showed a hydatidiform mole *in situ*, with very early myometrial invasion. No further treatment was required and the patient remains well nine years later.

Sections from the original vaginal biopsy showed a haemorrhagic nodule, at the periphery of which were scattered small numbers of rather pyknotic trophoblastic cells (figs 9 and 10). There were no chorionic villi and the appearances were those of a trophoblastic deportation nodule.

Case 79

This patient had a hysterectomy for hydatidiform mole at 24 weeks' gestation. Examination of the excised uterus showed a typical hydatidiform mole, with no evidence of invasion. Six weeks later she developed vaginal bleeding and was found to have a haemorrhagic nodule in the vagina. Needle aspiration yielded clumps of trophoblastic cells which were considered to be suspicious of choriocarcinoma. The patient was referred to Charing Cross Hospital for treatment. A further vaginal biopsy revealed typical hydropic chorionic villi. The diagnosis was therefore established as locally metastatic hydatidiform mole, and the patient was treated with chemotherapeutic agents. She remains well and free from trophoblastic disease eight years later.

The original histological sections were obtained

and examination showed not only fragments of trophoblast but also typical molar villi, the latter precluding a diagnosis of choriocarcinoma.

Case 83

Two months after stopping oral contraceptives this patient had a spontaneous abortion. Histological sections were reported as simple products of conception. Five weeks later further bleeding occurred and examination revealed a vaginal nodule. A biopsy was taken, and the specimen examined by a different pathologist who reported that the diagnosis was metastatic choriocarcinoma. The patient was referred to Charing Cross Hospital for further treatment, but before this was instituted the pathologist was informed of the previous biopsy and examined sections himself. He realized that there was hydatidiform degeneration of the chorionic villi and changed his diagnosis to metastatic hydatidiform mole. The patient remains well six years later.

The diagnosis of choriocarcinoma need not have been made in the first place. Although the appearance of some of the trophoblast in the vaginal deposit was similar to choriocarcinoma (fig 11) hydropic chorionic villi were also present (fig 12). As the original products of conception were morphologically small fragments this is an example of a 'transitional' mole with vaginal metastasis.

Of the five cases in which biopsies were taken, four of the vaginal nodules were true metastases of molar tissue while the fifth was an example of tropho-

blastic deportation. All the metastases behaved in a benign way, and the most disturbing aspect is the fact that a diagnosis of choriocarcinoma was either suggested or firmly made in four out of the five cases, the correct diagnosis being made in only one. The basic presumption seems to have been that the development of vaginal nodules in hydatidiform mole is in itself indicative of malignant change. This misconception is dangerous, and can easily lead to the patient receiving unnecessary surgical or cytotoxic therapy. The essentially benign nature of vaginal nodules has been stressed repeatedly (Haines, 1955; Bardawil *et al*, 1957; Thiele and Alvarez, 1962), and Dinh-De and Minh (1961) have published details of a patient with hydatidiform mole and recurrent vaginal nodules in whom recovery was complete. Hsu *et al* (1962) found vaginal metastases in eight out of 14 cases, with one death, and stated that metastases to the vagina did not carry a hopeless implication. Gore and Hertig (1967) considered that vaginal nodules following a normal pregnancy were virtually always choriocarcinoma, but in the case of hydatidiform mole, unless the trophoblast was very abundant or had the classical appearances of choriocarcinoma, it was better to assume that it was merely deported trophoblast.

To summarize, the presence of vaginal metastases in hydatidiform mole should not be regarded as evidence of malignancy, unless there is unequivocal histological confirmation. It is indefensible to institute potentially dangerous therapy for a simple

Fig 11

Fig 11 Fragment of trophoblast from a vaginal nodule in a patient with a 'transitional' hydatidiform mole. The histological appearances, with differentiated cytotrophoblast and syncytiotrophoblast, are not dissimilar to those of choriocarcinoma. H & E $\times$ 100.

Fig 12

Fig 12 Fragments of hydropic chorionic villi from the same vaginal nodule as that shown in figure 11, ruling out a diagnosis of choriocarcinoma. H & E $\times$ 60.

hydatidiform mole when conservative management of local metastases is sufficient, and the pathologist bears a considerable responsibility in his assessment of these lesions.

Choriocarcinoma

Choriocarcinoma can be defined as 'a malignant tumour occurring as a result of a gestation, and composed only of cytotrophoblast and syncytiotrophoblast, which, if not treated, will almost invariably cause death'. Clinically, the most remarkable feature of choriocarcinoma is that this highly aggressive malignant tumour is now eminently curable. Indeed, so successful may treatment be that, if the uterus is preserved, a subsequent normal gestation is possible (Bagshawe, 1969).

The typical histopathological appearances have

been so well described in the past (Teacher, 1903; Ewing, 1910; Park and Lees, 1950; Novak and Seah, 1954a; Ober *et al*, 1971; Park, 1971) that little more than a brief outline will be given here. Grossly there is remarkable consistency in the findings. The tumour nodule varies considerably in size, from 0.5 cm up to more than 5 cm in diameter, and is composed of a central brownish area of haemorrhage and necrosis with a surrounding rim of purple trophoblast. The nodules may be single or multiple (fig 13), deep in the myometrium, or projecting into the uterine cavity. At metastatic sites the same haemorrhagic nodular structure is still apparent; in the lung the nodules are often situated subpleurally, but rarely the tumour is entirely intra-vascular.

Microscopically the malignant trophoblast is situated at the periphery of the nodule and little is found in the central part. This is mainly due to the fact that, unlike any other tumour, choriocarcinoma contains no inherent stromal vasculature. The tumour cells thus rely on permeation of the 'host' blood vessels for nutrition, and these vessels are only present at the tumour-host interface. In this respect the malignant trophoblast of choriocarcinoma behaves in exactly the same way as normal trophoblast. The tumour tissue is usually organized into central cores of cytotrophoblast-like cells surrounded by a peripheral rim of syncytiotrophoblast-like cells with the latter often arranged around blood-filled spaces resembling the normal intervillous space (figs 14 and 15). Variation from this typical pattern occurs, and occasionally one or other element predominates, whilst in parts of most tumours the clear distinction between cytotrophoblast and syncytiotrophoblast is lost. Unlike normal trophoblast there is considerable variation in size and shape of nuclei, and nucleoli are often multiple. Mitotic activity is also variable, but rarely excessive. Although there is little myometrial necrosis, invasion through the uterine wall is particularly conspicuous. This invasion is very rarely directly through muscle fibres, but is almost entirely intra-vascular, and a striking feature of the uterine venous sinuses in choriocarcinoma is their great dilatation. The combination of the unique lack of tumour stromal vessels and permeation of dilated maternal vessels is associated with a high proportion of blood-borne metastases. The relative frequency of metastases at different sites in a necropsy study of 27 patients dying from choriocarcinoma (Elston, 1970) is shown in table I. It will be noted that in none of the cases was lymph node involvement found, and Park and Lees (1950) and Novak and Koff (1930) found lymph node metastases in only 6% and 4% respectively.

Fig 13 Hemisected uterus showing multiple dark haemorrhagic nodules of choriocarcinoma in the body and cervix.

Fig 14 Choriocarcinoma, composed of sheets of cytotrophoblast and syncytiotrophoblast, invading myometrium H & E $\times 100$.

Fig 15 Higher magnification of another choriocarcinoma. Note the organized pattern, with syncytiotrophoblast lining pseudo-intervillous spaces containing maternal red cells. H & E $\times 400$.

Organ	Percentage Involvement
Lung	80
Brain	40
Vagina	25
Liver	20
Kidney	20
Intestines	15

Table I Metastatic sites at necropsy in 27 patients with gestational choriocarcinoma

As a point of distinction from invasive mole, molar chorionic villi are absent. In one case in the series examined by Elston (1970) chorionic villi were seen in or close to the tumour. Those quite separate from the tumour were degenerate and surrounded by inflammatory cells; they appeared to be undergoing resorption (fig 16). The villus within the tumour was histologically well preserved with a

double layer of normal trophoblast around it: malignant trophoblast did not arise from the villus, nor did the villus appear to be invading the myometrium (fig 17). This choriocarcinoma occurred seven weeks after a spontaneous abortion, and no evidence of molar change was seen in the original products of conception. There is no reason why vestiges of the villi from the trophoblast of which the tumour has arisen should not occasionally persist, but the occurrence seems to be rare. MacRae (1951), Driscoll (1963) and Brewer and Gerbie (1966) have described very early choriocarcinomas found in otherwise normal placentas. In Driscoll's case there were no metastatic sequelae, but Brewer and Gerbie presented three patients, all of whom died from metastatic choriocarcinoma in which villi were not found. All these tumours arose from non-molar gestations. The arguments relating to the wisdom of

Fig 16

Fig 16 Degenerate, but not hydropic, chorionic villus by surrounded inflammatory cells, lying in the myometrium adjacent to a choriocarcinoma. *H & E* $\times 140$.

Fig 17

Fig 17 Chorionic villus lying close to an area of choriocarcinoma. The neoplastic trophoblast is not arising from the villus, nor is the latter invasive. Same case as figure 16. *H & E* $\times 100$.

retaining invasive mole as an entity separate from choriocarcinoma on the basis of its villous structure have already been discussed; suffice it to say that it seems illogical to use the phenomena described above in support of the 'villous' and 'avillous choriocarcinoma' concept, when the villi are an incidental finding. The presence of a number of degenerate villi, not obviously invasive in themselves, should not invalidate a diagnosis of choriocarcinoma in the face of separate sheets of typical invasive malignant trophoblast.

The Diagnosis of Trophoblastic Lesions in Uterine Curettings

Since the advent of accurate methods for estimating gonadotrophins and the introduction of cytotoxic

agents, there has been a decline in the use of histopathological methods in the management of established cases of trophoblastic disease (Hammond *et al*, 1967). However, in the majority of patients who develop trophoblastic disease an important presenting symptom is uterine bleeding, and the most widely used diagnostic tool in this situation is histological examination of uterine curettings. Indeed, curettings containing chorionic villi or fragments of trophoblast are among the commoner diagnostic problems in routine gynaecological histopathological practice. Most of the tissue is simple retained products of conception, but in some the trophoblast appears abnormal, and the possibility of choriocarcinoma must be considered. The histopathologist, therefore, continues to be faced with the problem of trophoblastic curettings, and

his report may have a profound effect on primary treatment. This is reflected in the material seen in the Charing Cross series, which was derived from over 30 hospitals in the United Kingdom.

The reliability of the diagnosis of choriocarcinoma from uterine curettings has been questioned by some authors (Novak, 1922; Mathieu, 1939), although in several reports (Teacher, 1935; Park and Lees, 1950; Sta. Cruz, 1959; Novak and Seah, 1954a; Novak and Woodruff, 1974) curettage was found to be useful in a proportion of cases. Because choriocarcinoma is rare in the United Kingdom most histopathologists have a limited experience, and there seems to be a tendency towards overdiagnosis, particularly in curetted material. This, on occasion, has led to patients receiving unnecessarily radical therapy, particularly operative surgery. It must not be forgotten that the majority of patients with trophoblastic disease are young and wish to bear children; the pathologist has a duty to ensure that he is not responsible for the unnecessary curtailment of this function.

The pathological material from the patients treated at Charing Cross Hospital has been used by Elston and Bagshawe (1972b) to define the histological criteria and suggest general principles for the reporting of uterine curettings in trophoblastic disease. They examined curettings from 54 patients; in 38 the curettings were obtained during follow up of a patient with hydatidiform mole, in 12 patients following a normal pregnancy and in four after a spontaneous abortion. Excluding curettings in which no trophoblastic tissue was found, three histological groups could be identified:

VILLOUS

In this study all the villous curettings came from postmolar cases, and the villi showed hydropic change with variable trophoblastic hyperplasia. Occasionally villi were inconspicuous and scanty.

SIMPLE OR SUSPICIOUS TROPHOBLAST

The appearances of the trophoblast in this category were of two main types. In one the fragments of

Fig 18 *Simple trophoblast. There are small fragments of trophoblast with pyknotic nuclei, but no clear differentiation into cytotrophoblast or syncytiotrophoblast. H & E $\times 120$.*

Fig 19 *Suspicious trophoblast. Although cytotrophoblast and syncytiotrophoblast can be identified separately, the overall pattern is disorganized. There is no invasion. H & E $\times 150$.*

trophoblast were small, and clear differentiation into cytotrophoblast and syncytiotrophoblast was poor (fig 18); nuclei were often hyperchromatic and irregular, appearances which could lead the unwary into a mistaken diagnosis of malignancy. In the other there were larger sheets of trophoblast, and differentiation into cytotrophoblast and syncytiotrophoblast was usually seen (fig 19). The trophoblast in some of these cases resembled that of choriocarcinoma, but in none of the curettings was there evidence of invasion. Chorionic villi were absent.

TROPHOBLAST DIAGNOSTIC OF CHORIO-CARCINOMA

Curettings were only considered to be diagnostic of choriocarcinoma when there was invasion of endometrium and myometrium by large sheets of trophoblast having a typical, well organized pattern. Nuclei were vesicular, with prominent and often multiple nucleoli. No chorionic villi were seen.

When the type of trophoblast in the curettings was

matched with antecedent gestation and subsequent trophoblastic disease several practical points emerged. In this series all the villous curettings were obtained in the follow up of a hydatidiform mole. Chorionic villi are not infrequently present in curettings taken after a normal term pregnancy or a spontaneous abortion, but they are virtually always degenerate, and the question of abnormal trophoblastic proliferation seldom arises. After a hydatidiform mole the problem is more difficult because of the undoubted malignant potential of molar trophoblast. Nevertheless, Elston and Bagshawe (1972b) considered that a diagnosis of choriocarcinoma must not be made in the presence of villous curettings. Most of the patients in this group pursued a relatively benign course, requiring only short courses of chemotherapy or no treatment at all, and in only a small proportion (10%) was a definite tissue diagnosis of choriocarcinoma subsequently established. This is not to say that the finding of villi should be ignored. This indicates that active trophoblastic proliferation is still continuing, and adequate

Fig 20 Hyperplastic trophoblast attached directly to myometrium. From a postmolar curetting which also contained molar villi. *H & E* $\times 90$.

Fig 21 Higher magnification of myometrium in figure 20, showing the typical giant cells of placental site reaction. *H & E* $\times 180$.

follow up should be carried out. Furthermore, since the presence of formed villi is an indication of a relatively more favourable prognosis, great care should be taken not to overlook them.

In the case of curettings containing simple or suspicious trophoblast the nature of the antecedent gestation was found to be of great importance. As with the villous group, if simple or suspicious curettings are obtained after the abortion of a hydatidiform mole, the findings should be interpreted with caution: careful follow up is essential, but a definite histological diagnosis cannot be made. If the preceding gestation was a normal pregnancy or a spontaneous abortion simple or suspicious trophoblast has a far more serious implication. In the series of Elston and Bagshawe all the patients in this group had malignant or potentially malignant disease needing chemotherapy, and it is a good working rule to assume that the presence of non-villous trophoblastic proliferation following a normal pregnancy or a spontaneous abortion means that the patient has developed choriocarcinoma unless proved otherwise.

A number of mononuclear and multinucleated trophoblastic cells is normally found in the endometrium and myometrium at the implantation site in normal gestations. Unfortunately, the same appearances may be mistaken for invasive choriocarcinoma in curettings following molar gestations. Although the trophoblastic infiltration can be unusually florid in a postmolar curetting (figs 20 and 21), there is no evidence to suggest that its presence has any sinister implications. The exaggerated form of placental site reaction, first described by Marchand (1898) as 'atypical choriocarcinoma' and later called 'syncytial endometritis' by Ewing (1910), presents a more difficult problem. Both Marchand and Ewing commented on the widespread permeation of the uterine musculature by giant mononuclear cells apparently derived from the syncytium; in Ewing's opinion the prognosis was much more favourable than that of typical choriocarcinoma. Others do not consider the lesion to be a true neoplasm (Novak and Seah, 1954b; Ober *et al*, 1971; Elston and Bagshawe, 1972b) but rather an abnormal persistence of placental site cells. Nevertheless, both clinically and histologically there are features which may closely mimic choriocarcinoma. In uterine curettings containing myometrium there may be numerous trophoblastic cells infiltrating between muscle bundles (fig 22) and in hysterectomy specimens these cells can extend out to the serosa. Indeed, in a patient at present being treated at Charing Cross Hospital similar cells were also present in one ovary, and in the face of such extensive spread it is difficult to exclude completely the

Fig 22 Myometrium in which there is an exaggerated placental site reaction with trophoblastic cells infiltrating between muscle bundles. H & E $\times 180$.

possibility of a malignant proliferation. Despite this, in most of the cases recorded in the literature, and in a small series studied personally, the condition is rarely if ever fatal.

One further source of diagnostic difficulty should always be considered, and that is the occurrence of 'new' pregnancy in the follow-up period of a spontaneous or molar abortion. This may initially be detected as a rise in gonadotrophin excretion, but if a curettage is performed it is important to remember that early trophoblast is histologically very similar to choriocarcinoma.

In the assessment of curettings containing trophoblastic tissue overdiagnosis rather than underdiagnosis is the commonest error, and the pathologist must be aware that a definite diagnosis of choriocarcinoma can only be made in a limited number of cases. In this sphere more than in many others, meticulous care must be taken both in the

Fig 23 Infiltrating choriocarcinoma on the left is surrounded by an intense inflammatory cell infiltrate. H & E $\times 100$.

examination of the tissue and in its correlation with clinical data. In most patients the correct management depends not only on the histological findings but also on a full consideration of clinical, hormonal and radiological factors.

Cellular Reaction Studies in Trophoblastic Disease

In many papers concerned with the histopathology of choriocarcinoma no mention is made of a cellular reaction to the tumours (Marchand, 1898; Teacher, 1903; Park and Lees, 1950; Hertig and Mansell, 1956; Smalbraak, 1957; Park, 1959), whilst in others the presence of inflammatory cells is described in occasional cases, with little or no reference to its possible significance (Ewing, 1910; Novak and Seah, 1954a; Hunter and Dockerty, 1955; Ober *et al*, 1971). In a discussion of the immunological aspects of the maternofetal relationship, with particular reference to choriocarcinoma, Strauss *et al* (1967) described a

patient with metastatic malignant trophoblast in the pulmonary vasculature (p 513). Collections of lymphocytes and plasma cells were present at points where tumour appeared to break through the vessel wall. The authors suggested that this cellular response may occur because of immunological recognition of cytotrophoblast at these sites, but concluded that supporting evidence was lacking. Conversely, the absence of an inflammatory cell reaction against deeply infiltrating or metastatic trophoblast in 30 cases of choriocarcinoma and invasive mole was cited by Iliya *et al* (1967) in support of their contention that choriocarcinoma behaves as a successful allograft.

Following an observation in 1966 that an intense cellular reaction was present in the hysterectomy specimens from several patients who had responded rapidly to chemotherapy, Elston published the preliminary results of a formal study of this phenomenon in 1969. Histological material from 38 patients with gestational choriocarcinoma was examined. The cellular infiltrates (fig 23) were composed of small and large lymphoid cells, plasma cells and histiocytes, with occasional eosinophil polymorphonuclear leucocytes. Neutrophil polymorphonuclear leucocytes were only rarely seen in these infiltrates, being found more commonly in areas of necrotic tumour. Two main cellular reaction groups could be identified, 'mild' and 'severe', and when the histological findings were correlated with response to treatment a remarkable difference between the two groups was found. Of the 29 patients in whom the primary tumour was examined, only six out of the 18 in the mild reaction group survived, against nine out of the 11 patients in the severe reaction group ($\chi^2 = 4$; 1df; $P = < 0.025$). It was concluded that there was a significantly better response to treatment in the patients with a severe cellular reaction. A more comprehensive study was then carried out, and the cellular reaction assessed in 40 patients with gestational choriocarcinoma, 10 patients with invasive mole and 13 with malignant teratoma trophoblast of testis or ovary (Elston and Bagshawe, 1973). Although found in eight of the 10 cases of invasive mole the cellular reaction was considered to have no clinical significance. The reaction to trophoblastic teratomata was generally poor, but there was a marked cellular infiltrate in one male patient who has enjoyed a sustained remission. In the patients with gestational choriocarcinoma the same significant difference in response to treatment persisted, and if the reaction to tumours at primary and metastatic sites was included the association was even stronger (18 out of 20 in the 'severe' group survived compared with five out of 20 in the 'mild' group). Other histological features,

such as tumour necrosis, ratio of syncytiotrophoblast to cytotrophoblast and degree of vascular invasion by tumour, were correlated with cellular reaction, but no significant associations were found, nor was there any correlation with such clinical factors as maternal age, gravidity, type of antecedent gestation, time interval between antecedent gestation and diagnosis and extent of metastases at diagnosis.

It is now possible to bring these results up to date. None of the patients included in the original series has died, and the minimum follow-up period from the end of treatment is five years. Sections from an additional 17 patients have been examined, bringing the total to 57. The intensity of the cellular reaction to tumours at different sites is shown in table II. There are 33 patients in the 'mild' reaction group and 24 in the 'severe' group, and the number of survivors is, respectively, 10 and 21 (table III). Table IV shows the relationship between cellular reaction and response to treatment in the 42 patients in whom the primary tumour was removed before

treatment with cytotoxic agents. These results continue to confirm that the patient has a significantly better chance of surviving if there is a marked cellular reaction to the tumour tissue. Elston (1970) has also made a study in material obtained at necropsy, and found only one case out of 17 in which the cellular reaction could be placed in the 'severe' group.

Little attempt has been made by others to confirm these findings. Park (1971) has carried out an investigation based on material in the UK Registry for Diseases of Trophoblast. He examined sections from either the excised uterus or necropsy material in 50 patients with choriocarcinoma, and showed that a cellular reaction was present in 45, being marked in 20, with a general tendency for non-fatal cases to have a more pronounced reaction than fatal ones. Mogensen and Olsen (1973) found a cellular reaction in 22 out of 23 patients studied, with a significantly better response to treatment in those patients with a moderate or marked reaction.

It is clear from these studies that, contrary to the findings of Iliya *et al* (1967), a cellular infiltrate of variable degree is present in many cases in the tissues around deposits of choriocarcinoma, both primary and metastatic. There also seems to be little doubt that response to treatment is more favourable in the presence of an intense reaction. The biological significance of the cellular infiltrates is less easy to explain from the morphological appearances alone. The cells participating in the reactions are certainly the same as those seen in cell-mediated immune mechanisms (Waksman, 1960) and solid allograft rejection (Gowans, 1965), and Elston and Bagshawe (1973) have suggested that they represent an attempt at tumour rejection on an immunological basis. If this is correct, then there are three possible sources for a presumed antigen. Choriocarcinoma might contain tissue specific antigens for trophoblast, and although such antigens are thought to be present in normal human (Krieg, 1972) and animal trophoblast (Beer, *et al*, 1972), they have not yet been conclusively demonstrated in malignant trophoblast. Secondly, antigens related to malignant transformation may be expressed (Laurence and Neville, 1972), but again there has been no convincing evidence in support of this. It is of interest in this context that similar cellular reactions occur in other human tumours, particularly gastric carcinoma (Black *et al*, 1954) and carcinoma of breast (Black *et al*, 1956). Finally, since choriocarcinoma is, in effect, a malignant allograft, it may also exhibit individual specific or transplantation antigens, inherited from the male parent of the antecedent gestation.

The evidence in this area is conflicting, and it is

Site	Intensity of Cellular Reaction		
	Mild	Severe	Total
Primary	26	17	43
Metastatic	6	5	11
Primary and Metastatic	1	2	3
Total	33	24	57

Table II Intensity of cellular reaction at primary and metastatic sites in 57 cases of gestational choriocarcinoma

Response to Treatment	Intensity of Cellular Reaction		
	Mild	Severe	Total
Incomplete—all died	23	3	26
Complete remission	10	21	31
Total	33	24	57

$$\chi^2 = 16.09; 1df; P = < 0.001$$

Table III Comparison of cellular reaction to gestational choriocarcinoma in two groups of patients: free from tumour and dying during treatment

Response to Treatment	Intensity of Cellular Reaction		
	Mild	Severe	Total
Incomplete—all died	15	3	18
Complete remission	9	15	24
Total	24	18	42

$$\chi^2 = 7.05; 1df; P = < 0.01$$

Table IV Comparison of cellular reaction to the primary tumour removed before chemotherapy in two groups of patients with gestational choriocarcinoma: free from tumour and dying during treatment

important to remember that in none of the studies so far have ABO blood group substances or HL-A antigens been measured in tumour tissue, but in the red cells, leucocytes and serum of those being examined. Various authors have studied the blood groups of patients with trophoblastic disease. Schmidt and Hertz (1961) found no variation from the normal ABO groups in 28 patients and a similar finding was reported by Lewis (1973) in a study of 31 patients and their families. Conversely, Llewellyn-Jones (1965) showed a shift away from group O towards groups A and AB in Malaysian Chinese patients with trophoblastic disease, while in a later study from Singapore Dawood *et al* (1971) found a significant increase in blood group A in patients with choriocarcinoma. Bagshawe *et al* (1971) have shown that choriocarcinoma may arise from conceptions which are Rh or ABO incompatible with the host, with an excess risk associated with A ♀ × O ♂ matings compared with A ♀ × A ♂ matings (Bagshawe, 1973). Furthermore, patients of group AB appear to have a particularly high mortality, a point also noted by Dawood *et al* (1971).

Mogensen and Kissmeyer-Nielsen (1968, 1971) have studied HL-A data in patients with choriocarcinoma and concluded that generalized disease occurs when there is compatibility between host and conceptus at one or both HL-A loci, with only localized disease when there is patient-husband incompatibility at both loci. This has not been confirmed by other workers and in most series a substantial proportion of patients with choriocarcinoma demonstrate HL-A incompatibility with the antecedent gestation (Rudolph and Thomas, 1970; Lawler *et al*, 1971; Lewis and Terasaki, 1971). Bagshawe (1973) has concluded that although there is an indication from ABO blood group studies that genetic factors may play a part in the causation of choriocarcinoma, the immunological implications are unclear, and the HL-A data are remarkable for the apparent lack of effect of these antigens. Because of insufficient data it has not so far been possible to correlate ABO blood group and HL-A status with cellular reaction, and this and a search for the presence of antigens in tumour tissue itself are obvious areas for further investigation.

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