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Gestational trophoblastic diseases

Report of a
WHO Scientific Group

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CORRIGENDA

Page 58, lines 23–24

Delete: hydroxyurea + methotrexate + mercaptopurine
Insert: hydroxycarbamide + methotrexate + mercaptopurine

Page 64, lines 4–5

Delete: Days 2–8 methotrexate 50 mg i.m. or i.v (1 mg/kg max. 10 mg)
Insert: Days 2–8 methotrexate 50 mg i.m. or i.v (1 mg/kg max. 70 mg)

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WHO SCIENTIFIC GROUP ON GESTATIONAL TROPHOBLASTIC DISEASES

Geneva, 6–10 December 1982

*Members**

Dr H. Atrash, American University of Beirut, Ministry of Health of Bahrain, Manama, Bahrain

Dr D.P. Goldstein, New England Trophoblastic Disease Center, Boston Hospital for Women, Harvard Medical School, Boston, MA, USA

Dr D.A. Grimes, Pregnancy Epidemiology Branch, Reproductive Health Division, Center for Health Promotion and Education, Centers for Disease Control, Atlanta, GA, USA

Dr T.A. Junaid, Department of Pathology, University College Hospital, University of Ibadan College of Medicine, Ibadan, Nigeria

Dr S.J. Kim, Department of Obstetrics and Gynaecology, Catholic Medical Center, St Mary's Hospital, Seoul, Republic of Korea

Dr S.D. Lawler, Section of Human Genetics, Institute of Cancer Research, Royal Marsden Hospital, London, England

Dr S.S. Ratnam, Department of Obstetrics and Gynaecology, National University of Singapore, Kandang Kerbau Hospital for Women, Singapore (*Chairman*)

Dr Sung Hung Zhao, Department of Obstetrics and Gynaecology, Capital Hospital, Beijing, China

Dr A.E. Szulman, Department of Pathology, Magee Women's Hospital, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Secretariat

Dr K.D. Bagshawe, Department of Medical Oncology, Charing Cross Hospital Medical School, London, England (*Temporary Adviser*) (*Rapporteur*)

Dr E.W. Wilson, Medical Officer, Special Programme of Research, Development, and Research Training in Human Reproduction, WHO, Geneva, Switzerland (*Secretary*)

* Unable to attend: Dr J. Lewis, Jr, Memorial Hospital for Cancer and Allied Diseases, New York, NY, USA.

GESTATIONAL TROPHOBLASTIC DISEASES

Report of a WHO Scientific Group

1. INTRODUCTION

Gestational trophoblastic diseases present a series of unique problems in biology and clinical practice. The trophoblast itself is the first tissue to differentiate in the early embryo and becomes extra-embryonic with the formation of the placenta, forming the fetal side of the interface with maternal blood and tissue. The trophoblastic diseases are either tumours or conditions that predispose to tumours. These tumours are unique, being allografts arising from a conceptus that invade the tissues of the mother. Since they are associated with pregnancy they affect women of reproductive age, at a time when their social commitments are at their peak.

1.1 Gestational trophoblastic diseases

Gestational trophoblastic diseases include hydatidiform mole, a form of conceptus which may have no serious sequelae, and other diseases such as choriocarcinoma, which, without specific treatment, is one of the human cancers that progresses most rapidly to a fatal outcome. However, choriocarcinoma was the first human cancer to respond frequently to chemotherapeutic agents with the possibility of a cure even when the cancer had become widely disseminated.

Choriocarcinoma can apparently arise from any human conceptus whether hydatidiform mole, spontaneous or induced abortion, ectopic pregnancy, stillbirth, or a normal live, full-term birth. However, the risk of choriocarcinoma is about one thousand times greater after hydatidiform mole than it is after normal pregnancy. The risk of choriocarcinoma is therefore greatly influenced by the risk of a conception resulting in hydatidiform mole (HM). It has been reported that the incidence of HM varies greatly between countries, but the reasons for these differences are largely unknown.

Invasive mole is a much more common but less serious sequel to HM than choriocarcinoma, and is usually recognized within six months of the evacuation of a mole. It may closely mimic choriocarcinoma, producing secondary lesions particularly in the vagina and lungs, but, unlike choriocarcinoma, it can regress spontaneously. It is distinguished from choriocarcinoma morphologically by the presence of villi which are not seen in choriocarcinoma, and by the fact that it generally fails to progress after hysterectomy, unlike choriocarcinoma. Thus, HM may give rise to two distinct lesions, one with a low potential to kill and the other with a high potential, but in their early stages they may be indistinguishable without a major surgical procedure.

Since non-molar pregnancies do not give rise to invasive mole, a trophoblastic tumour arising from a non-molar pregnancy is a choriocarcinoma or less commonly a placental site trophoblastic tumour. Placental site trophoblastic tumour is a recently introduced term but the lesion has been known for many years under various names such as chorioma, atypical choriocarcinoma, or trophoblastic pseudotumour.

Just as placental site tumour has become more clearly recognized in the past few years, our understanding of HM has also increased. Classical mole, now called complete mole, has long been recognized as being a product of conception with an appearance similar to a bunch of grapes, and at the morphological level the absence of a fetus and the hydropic state of the villi are accompanied by undue proliferation of the trophoblast. But conceptions have also been recognized in which a fetus is present, and in this case the placenta exhibits less extensive hydatidiform changes of the villi with variable trophoblastic hyperplasia; these are now called partial moles. In addition, there has been difficulty in assessing the significance of lesions where hydropic change occurs in the placenta of an aborted conceptus, without trophoblastic hyperplasia.

Cytogenetic studies have demonstrated conclusively that complete mole can be clearly distinguished from partial mole. Following this advance, it has been possible to redefine the morphological characteristics of complete and partial mole so that even without cytogenetic studies the distinction between them can be made more accurately than was possible a few years ago.

Unfortunately, most of the data relating to HM were collected before this distinction was possible so that the relative incidence of complete and partial mole in various populations is unknown. The

precise risk of developing invasive mole or choriocarcinoma after complete and partial moles is also uncertain, although it seems probable that the risk after partial mole is much the lower.

1.2 The size of the problem

The incidence of HM reported in the literature ranges from 0.5 to 8.3 cases per 1000 live-births. If it is assumed that there is one HM for every 1000 live-births, then with 126 million live-births throughout the world 126 000 HM can be expected annually. The actual figure is expected to be much higher than this.

Morbidity due to anaemia may occur in about a half of these women. A minimum of 10% of HM patients require chemotherapy for choriocarcinoma and invasive mole. About 2 out of 100 000 pregnancies that result in childbirth lead to choriocarcinoma and a similar number of cases arise following abortions. Overall, an estimate of 20 000 patients per annum requiring chemotherapy for choriocarcinoma or invasive mole is probably conservative and the figure could be as high as 40 000 per annum.

1.3 Detection and management of choriocarcinoma

One of the main long-term objectives of cancer research is to develop methods for both the biochemical detection of cancer and its biochemical or chemotherapeutic eradication. In the case of trophoblastic tumours these objectives can already be achieved since the necessary knowledge and means to control most of these tumours have existed for many years. However, many patients still fail to benefit.

The problem of detecting pre-symptomatic choriocarcinoma after non-molar pregnancies is too difficult to be tackled even in advanced societies. Even if fully effective, probably only one choriocarcinoma in about 50 000 pregnancies would be detected, and given present resources this would not be practicable.

The problem of detection after HM is however quite different and HM can be regarded as the ideal model for a cancer-screening programme. Thus there is a well-defined population of young women who are at a high risk of a potentially fatal lesion; but if it is detected within the appropriate time by relatively low-cost, reproducible, and widely available tests for human chorionic gonadotrophin (hCG), this threat to life can be eradicated in almost every case.

However, this procedure has so far involved repetitive examination over a period of 1–2 years and while this may be feasible in an advanced society great difficulties are involved in developing countries.

1.4 Prophylactic chemotherapy

In the early 1960s it was suggested that an alternative to screening was to regard HM as a precancerous lesion and to give chemotherapy to all patients soon after a mole was evacuated. Justification for this approach depends on the level of risk of malignant sequelae, the effectiveness of prophylactic treatment in avoiding the need for subsequent therapy, the risk of inducing drug resistance, and the short-and long-term risks to health.

1.5 Contraception

Another example of the need for data concerns contraception. A new pregnancy following soon after hydatidiform mole or after apparently successful treatment for invasive mole or choriocarcinoma can result in difficulties in distinguishing between the new pregnancy and trophoblastic disease. The methods of contraception used by these patients is important and questions have been raised about both oral contraception and intrauterine devices. Whether these suspicions are soundly based depends on the validity of the data for the population studied and on its extrapolation to other populations.

2. DEFINITION OF TERMS

The Scientific Group noted that there is considerable confusion in the literature concerning the terminology of gestational trophoblastic diseases. In addition, there has been a tendency to regard histopathological and clinical terms as interchangeable. The Group therefore made the following recommendations for histopathological and clinical terminology in an attempt to standardize the reporting of data.

It was recognized that histological definitions for hydatidiform mole, invasive mole, and choriocarcinoma already appear in the

International Histological Classification of Tumours (*1*). However, new evidence has created a need to amplify the definition of hydatidiform mole to distinguish between its varieties.

2.1 Histopathological entities

Hydatidiform mole. A general term that includes two distinct entities, complete hydatidiform mole and partial hydatidiform mole; the features common to both forms are a hydropic state of some or all villi and trophoblastic hyperplasia.

Complete hydatidiform mole. An abnormal conceptus without an embryo–fetus, with gross hydropic swelling of the placental villi and usually pronounced trophoblastic hyperplasia of both layers. The villous swelling leads to central cistern formation with a concomitant compression of the maturing connective tissue that has lost its vascularity.

Partial hydatidiform mole. An abnormal conceptus with an embryo–fetus that tends to die early, with a placenta subject to focal villous swelling leading to cistern formation, and with focal trophoblastic hyperplasia usually involving the syncytiotrophoblast only. The unaffected villi appear normal and vascularity of the villi disappears following fetal death.

Invasive mole. A tumour or a tumour-like process invading the myometrium and characterized by trophoblastic hyperplasia and persistence of placental villous structures. It commonly results from complete hydatidiform mole and may do so from partial hydatidiform mole. It does not often progress to choriocarcinoma. It may metastasize but it does not exhibit the progression of a true cancer and it may regress spontaneously. The following terms are synonyms that the Group considered should no longer be used: malignant mole, molar destruens, chorioadenoma destruens.

Gestational choriocarcinoma. A carcinoma arising from the trophoblastic epithelium that shows both cytotrophoblastic and syncytiotrophoblastic elements. It may arise from conceptions that give rise to a live-birth, a stillbirth, an abortion at any stage, an ectopic pregnancy, or a hydatidiform mole, or it may possibly arise *ab initio*. Chorionepithelioma is a synonym that the Group considered should no longer be used.

Placental site trophoblastic tumour. A tumour that arises from the trophoblast of the placental bed and is composed mainly of cytotrophoblastic cells. It encompasses lesions of low- and high-grade

malignancy. Trophoblastic pseudotumour is a synonym that the Group considered should no longer be used.

The following conditions may be involved in the differential diagnosis of trophoblastic diseases, but they do not themselves constitute trophoblastic disease.

Placental site reaction. A term that refers to the physiological finding of trophoblastic and inflammatory cells in the placental bed. The term "syncytial endometritis" has sometimes been applied to this process but it is inappropriate and confusing and the Group recommended that it should no longer be used.

Hydropic degeneration. A condition of placental villi characterized by dilatation and increased fluid content or liquefaction of the villous stroma, but without trophoblastic hyperplasia. It has to be distinguished from hydatidiform mole and is not associated with an increased risk of neoplastic sequelae. Molar degeneration, hydatidiform degeneration, and hydropic change are synonyms that the Group considered should no longer be used.

The following terms were considered by the Group to have no further use.

Transitional mole. A term that has been applied in the past to conceptions with a recognizable embryo or gestational sac and hydatidiform villi.

Villous choriocarcinoma. A term that was suggested as a name for lesions that show villi but metastasize. These lesions are in fact invasive moles and therefore villous choriocarcinoma is superfluous.

2.2 Clinical terms

Although it is recognized that invasive mole and choriocarcinoma show important biological and prognostic differences, clinical management of these conditions often has to proceed without a histopathological diagnosis and this has resulted in the use of terms intended to embrace both conditions. It is important, however, that these terms should closely reflect the histopathological entities and their natural histories wherever possible.

Gestational trophoblastic disease. A general term that covers hydatidiform mole, invasive mole, placental site trophoblastic tumour, and choriocarcinoma. It therefore includes both benign and malignant conditions in variable proportions.

Gestational trophoblastic tumour. A disease-state in which there is clinical evidence of invasive mole or choriocarcinoma. This cate-

gory is further subdivided according to antecedent pregnancy, as post-mole, post-abortion, post-delivery, or unknown pregnancy. The Group considered that "gestational trophoblastic tumour" should replace "gestational trophoblastic neoplasia" since invasive mole is not regarded as a true neoplasm.

Metastastic trophoblastic tumour. A disease-state in which there is clinical evidence of invasive mole or choriocarcinoma that has extended beyond the body of the uterus.

3. EPIDEMIOLOGY

Most of the information about the epidemiology of gestational trophoblastic diseases is discussed under specific disease entities; this section is limited to a consideration of general issues.

3.1 Limitations of published data

The epidemiology of gestational trophoblastic diseases (GTD) is poorly understood. Three obstacles limit the interpretation of most published studies. First, many reports lack a clear, precise, and reproducible case definition of the disease or diseases in question. Most studies antedate the discovery in 1977 (*1a*) that HM encompasses two different entities with different etiologies; therefore previous classifications of HM have become obsolete. An additional problem is the confusion between hydropic degeneration and HM. Again, the diagnosis of invasive mole (IM) requires histological evidence of myometrial penetration; since hysterectomy is infrequently performed as therapy, this diagnosis is often not possible. Similarly, presumed cases of choriocarcinoma can be treated with chemotherapy without a previous histological diagnosis.

Secondly, published reports are subject to errors in ascertaining cases of GTD. Overreporting of pregnancies involving gestational trophoblastic disease relative to other pregnancies can occur in hospital-based studies, particularly in less developed countries, because "problem pregnancies" or cancer cases are more likely to receive hospital care than are uncomplicated deliveries, which may occur routinely at home (*2*). Underreporting of cases of GTD may also be common. HM may be spontaneously expelled in many women who never receive medical attention. Likewise, choriocarci-

noma may not be diagnosed in women who die without medical care or autopsy.

Thirdly, reported rates of GTD are difficult to interpret because different denominators (the populations at risk) are used in published studies. Since only women who have been pregnant are at risk of GTD, traditional census statistics, which do not take fertility levels into account, are inappropriate for use in calculating incidence rates. The preferred denominator for women at risk of GTD is all women who have conceived.

Since this number is rarely known, several approximations have been used as denominators when calculating incidence rates. "Pregnancies" usually includes live-births, stillbirths, known abortions, and ectopic pregnancies, and represents the closest approximation to the population at risk. "Deliveries" is less desirable as a denominator, since it excludes a large and unknown number of conceptions that terminate because of induced or spontaneous abortion, as well as a smaller number of ectopic pregnancies. "Live-births" excludes still more conceptions at risk; nevertheless, "live-births" may be the only or the most complete information available. Because different denominators have been used in calculating incidence rates, comparison of these rates between studies may be misleading. Because denominators underestimate the size of the population at risk, the estimates of the incidence of GTD will be too high.

Methods of determining the denominators for calculating incidence rates also vary. The use of births or live-births in hospitals as the denominator, especially in regions where childbirth at home is customary, may account in part for the high rates of GTD reported from less developed countries. In addition, the use of surveys that depend on women's recall may be equally unreliable (*3*). Population-based studies that rely on a centralized pathology institute or comprehensive hospital surveillance (*4, 5*) should provide the most accurate estimates of the incidence of gestational trophoblastic disease.

3.2 Geographical variation in the incidence of gestational trophoblastic disease

Although large regional differences in the incidence of HM have been reported (Tables 1 and 2), this variation may be partly due to the methodological problems cited previously. For example, most reports of high rates of HM in Asia and Latin America come from single hospital studies. If, however, incidence rates from population-

based studies in different regions of the world are compared, a different pattern emerges (Table 1).

Population-based studies in North America (*6–8*), southern Asia (*9*), and Europe (*5*) have reported rates that do not differ strikingly from one another. However, data from Japan (*10*) indicate a higher rate. Paradoxically, one such report from Latin America (*5*) described the lowest rate. Overall, rates in these population-based studies range from 0.2 to 1.96 cases per 1000 pregnancies. On the other hand, incidence rates from hospital-based studies range from 0.7 to 11.6. Thus, population-based estimates of the incidence of hydatidiform mole tend to be lower and more uniform from region to region than are estimates derived from hospital studies.

The evidence for large regional differences in the incidence of choriocarcinoma appears to be limited (Table 2). Similar rates have been reported in population-based studies from countries in Latin America (0.2 cases per 10 000 pregnancies) (*11*) and Europe (0.2) (*4*), but not from studies in Japan (0.83) (*10*). Problems with case definition and ascertainment, use of different denominators, and use of different study intervals make a clear understanding of the incidence of GTD throughout the world difficult to achieve.

3.3 Temporal trends

Information on temporal trends in the incidence of hydatidiform mole is limited and conflicting. In two hospitals in the United States of America between 1930 and 1964, the incidence of hydatidiform mole declined during the Second World War, then rose later to surpass the pre-war rate (*12*). Among Jewish women in Israel from 1950 to 1965, the incidence steadily increased (*13*). Among indigenous Greenlandic women in the period 1950–74, the incidence increased significantly after 1965 (*7*). From 1970 to 1977, the incidence of hydatidiform mole varied in the United States of America, but the data are inadequate to document temporal trends (*8, 9*).

Data on temporal trends in choriocarcinoma are even more limited. In Israel, the incidence of choriocarcinoma decreased significantly between 1950 and 1965: by 1960–65, the rate was less than one-third that of 1950–54 (*14*). To what extent these changes and those noted for hydatidiform mole are a result of the evolution of diagnostic and classification techniques for GTD is unknown.

Table 1. Examples of hydatidiform mole incidence by region

	Country or territory	Reference	Period of study	Rate per 1000		
				Pregnancies[a]	Deliveries[b]	Live-births
Population-based studies						
Latin America	Paraguay	(*5*)	1960–69	0.2	—	—
North America	Canada	(*6*)	1969–73	—	—	0.7
	Greenland	(*7*)	1950–74	—	1.2	—
	USA	(*8*)	1970–77	1.1	—	—
Asia	Japan	(*10*)	1974–80	1.96	—	3.02
	Singapore	(*9*)	1963–65	—	1.2	—
Europe	Norway	(*15*)	1953–61	—	0.8	—
	Sweden	(*4*)	1958–65	0.6	—	—
Hospital-based studies						
Africa	Nigeria	(*16*)	1969–73	—	5.8	—
	Nigeria	(*17*)	1974–77	—	2.6	—
	Nigeria	(*18*)	1966–75	—	1.7	—
	Uganda	(*19*)	1967–70	—	1.0	—
Latin America	Jamaica	(*20*)	1953–67	—	1.0	—
	Mexico	(*21*)	1961–65	4.6	—	—
	Mexico	(*22*)	—[d]	1.6	1.9	2.0
	Venezuela	(*23*)	1939–68	0.9	1.1	1.1
North America	USA	(*12*)	1930–65	0.7	—	—
	(Alaska)	(*24*)	1969–74	—	3.9	—
	USA	(*25*)	1932–42	—	0.5	—
	(Hawaii)	(*26*)	1951–65	0.8	—	—
	(Hawaii)	(*27*)	1950–70	—	—	1.0
	(Hawaii)	(*28*)	—[d]	—	—	4.6

Asia	China (Province of Taiwan)	(*30*)	1951–60	—	8.0	—
	Indonesia	(*31*)	1962–63	10.0	11.6	—
	Iraq	(*34*)	1960–64	4.5	—	—
	Islamic Republic of Iran	(*32*)	1964–65	7.8	10.6	—
	Islamic Republic of Iran	(*33*)	1970–75	3.2	—	3.7
	Israel	(*13*)	1950–65	—	—	0.8
	Japan	(*29*)	1972–77	1.9	2.6	—
	Lebanon	(*35*)	1956–60	2.6	—	—
	Malaysia	(*36*)	1972–76	—	1.5	—
	Philippines	(*37*)	1955–57	1.1	—	—
	Thailand	(*38*)	1966–72	2.8	2.9	—
Europe	Italy	(*39*)	1961–74	—	0.8	—
Oceania	Australia	(*40*)	1940–59	—	2.4	—
	Australia	(*41*)	1950–66	0.9	1.0	—

[a] Recognized pregnancies; usually includes live-births, stillbirths, known abortions, and ectopic pregnancies
[b] Includes live-births and stillbirths.
[c] Definition of "live-births" usually not stated.
[d] Not specified.

Table 2. Examples of choriocarcinoma incidence by region

Author	Country or territory	Reference	Period of study	Rate per 10 000		
				Pregnancies[a]	Deliveries[b]	Live-births[c]
Population-based studies						
Latin America	Paraguay	(*11*)	1960–69	0.2	—	—
North America	Canada	(*6*)	1969–73	—	—	0.4
	Jamaica	(*42*)	1958–73	—	—	1.4
	Puerto Rico	(*43*)	1950–65	—	0.3	—
Asia	Japan	(*10*)	1964–80	0.53	—	0.83
	Singapore	(*44*)	1959–64	—	—	1.1
	Singapore	(*45*)	1960–70	—	2.3	—
Europe	Sweden	(*4*)	1958–65	0.2	—	—
Hospital-based studies						
Africa	Nigeria	(*18*)	1966–75	—	9.9	—
Latin America	Mexico	(*21*)	1961–65	3.5	—	—
	Mexico	(*22*)	—[d]	0.2	0.3	0.3
North America	USA	(*46*)	1959–64	0.5	0.6	—
	USA	(*12*)	1930–65	0.3	—	—
Asia	China (Province of Taiwan)	(*30*)	1951–60	—	20.2	—
	Hong Kong	(*2*)	1953–61	—	7.5	—
	India	(*47*)	1955–64	19.1	—	—
	Indonesia	(*31*)	1962–63	15.3	17.7	—
	Israel	(*14*)	1950–65	—	—	0.5
	Japan	(*29*)	1972–77	1.2	1.7	—
	Philippines	(*48*)	1950–62	8.7	—	—
	Philippines	(*49*)	1970–74	—	—	1.7
	Thailand	(*38*)	1966–72	6.3	6.5	—
Oceania	Australia	(*41*)	1950–66	0.7	0.8	—

[a] Recognized pregnancies; usually includes live-births, stillbirths, known abortions, and ectopic pregnancies.
[b] Includes live-births and stillbirths.
[c] Definition of "live-births" usually not stated.
[d] Not specified

3.4 Recommendations for research

Epidemiological research

It is evident that data reflecting the causation and geographical incidence of trophoblastic diseases are very inadequate, and the following studies are suggested to try to correct this deficiency.

(1) Case–control studies should be undertaken to investigate the etiology of gestational trophoblastic diseases. This approach is particularly useful for studying diseases with a low incidence. All cases of hydatidiform mole should be classified as complete or partial on the basis of microscopic morphology. Where feasible, cases of hydatidiform mole should receive genetic investigation. The participation of several collaborating centres would increase the size and power of such case–control studies.

(2) To determine the incidence of gestational trophoblastic tumours after hydatidiform mole, collaborative prospective cohort studies should be done. Participating centres should have a large number of cases of hydatidiform mole, the capability for accurate classification of moles, and the capability for high rates of patient follow-up.

(3) To provide useful information on the incidence of gestational trophoblastic diseases in different geographical regions, population-based studies should be performed. For calculating incidence rates, the denominator (the population at risk) should include all women known to have conceived during a given time interval. Alternatively, the denominator could be limited to women who have had live-births, stillbirths, or induced abortions registered through vital statistics during a given time interval. Cases of gestational trophoblastic disease should be identified through a centralized registry or other comprehensive means of ascertainment. Estimates of the incidence of gestational trophoblastic disease derived from hospital-based studies are unreliable and, in general, should not be used.

4. HYDATIDIFORM MOLE

The level of understanding of hydatidiform mole and its clinicopathological features before the impact of recent advances in cytogenetics has been presented in several comprehensive reviews

(*50–53*). The common features of HM were gross swelling of placental villi and the presence of trophoblastic hyperplasia. However, it is evident that there has been confusion as to what constitutes HM since the grossly visible oedema of the placental villi has often been used as the sole criterion of "hydatidiform change". A preferable term for this gross appearance is hydropic change and the term "hydatidiform change" if used at all should be confined to descriptions of the histological findings in HM.

The morphological definition of HM that is now becoming accepted (*54*) is based upon hyperplasia of the trophoblast, while oedema of the placental villi alone, whether gross or microscopic, is of secondary importance (*53, 55*). There is no evidence that abortions with oedematous villi but no trophoblastic hyperplasia carry a greater risk of choriocarcinoma than a normal conception.

4.1 The forms of hydatidiform mole (HM)

It has long been known that there is much heterogeneity in HM, but only as a result of cytogenetic studies is a clear distinction now possible. The two principal forms are described as complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM). The cytogenetic distinction between these has facilitated a clearer definition of their morphological features (*1a, 56*).

4.1.1 *Complete hydatidiform mole (CHM)*

This is the classical mole bearing some resemblance to a "bunch of grapes". It is now known to result from the fertilization of an egg from which the nucleus has been lost or inactivated. Fertilization occurs by a single sperm bearing a 23 X set of chromosomes which duplicates to 46 XX so that most complete moles are homozygous, female, and androgenetic in origin. Less frequently, fertilization takes place with two spermatozoa, resulting in either a 46 XX or a 46 XY chromosome constitution (*1a, 57–60*). In either case, the conceptus is a paternally derived parthenogenome that is a total allograft in the mother. Biochemical markers have been used to confirm the cytogenetic findings (*59–62*).

Complete moles have been identified in elective abortion material from four weeks of development, after which time swelling of the

villi occurs rapidly resulting in apparent compression of the peripheral villous mesenchyme and the formation of villous cisterns (*56, 63*). At the same time hyperplasia is observed in both the cytotrophoblastic and syncytial elements, and although it is more marked in some villi than in others and more marked in some moles than in others, it is a relatively general process.

Another important feature of CHM is the absence of an embryo which dies at an early stage before the placental circulation is established. The vessels in the villi therefore may not be prominent and the older villi often become avascular. The vessels that are identified do not contain fetal (nucleated) erythrocytes. New villi continue to form during the life of CHM so that there is continued formation of vasculogenic mesenchyme while cistern formation is a staggered process.

Experiments on immunologically deficient mice in which only choriocarcinomas behaved as malignant tumours (*64*), suggest that the complete hydatidiform mole and invasive mole are not of themselves malignant, in contrast to choriocarcinoma. Nevertheless it is clear that CHM has a much higher potential to give rise to choriocarcinoma than a normal pregnancy.

Complete mole with twin fetuses is rare, although the incidence is not precisely known. Dizygotic twin pregnancies in which there was a normal placenta associated with a fetus and a separate molar mass have been reported (*65*), and further cases have been reported subsequently. Twin pregnancies with mole including CHM (46 XX) and fetus (46 XY) have been reported (*28, 56, 63, 66*). The fetus may be aborted but occasionally reaches term. Where a fetus is present it is important that every effort should be made to distinguish between a CHM with twin fetuses and PHM, since the potential for progressive disease may be much less with the latter.

4.1.2 *Partial hydatidiform mole (PHM)*

In one study (*1a*) PHM was identified on the basis that the swelling of the villi did not affect the whole placenta, that there was evidence of an embryo–fetus, and that the karyotype was either normal, trisomic, or triploid. Subsequent studies (*56, 63*), using both microscopy and cytogenetics, indicate that PHM showing trophoblastic hyperplasia and cistern formation was found only among triploid conceptuses. Cytogenetic and biochemical studies show that

maternal genes are present in PHM and that cases identified as suspected molar pregnancies are more likely to have arisen by diandry (one maternal and two paternal sets of chromosomes), than by digyny (two maternal and one paternal set of chromosomes) (*61, 67*).

The morphology of PHM (*63, 68*) is a mosaic of seemingly normal small villi and villi that slowly replicate the sequence of accumulation of fluid from oedema to cistern formation as seen in complete moles. In examples older than 18–20 weeks a peculiar type of cistern, with a maze-like outline is sometimes seen. If the fetus is alive, the vessels contain fetal (nucleated) red blood cells, both in the normal and in the oedematous villi, including those with cisterns. Irrespective of the fate of the fetus, there is a crinkling or scalloping of the villous outlines from the earliest stages that is quite characteristic and unique for triploid partial moles; it is apt to become exaggerated by fibrosis following fetal death, but it is often the most striking feature upon general view. Another highly characteristic feature is the presence of stromal trophoblastic inclusions (*69*).

Because of the mosaic-like pattern of the partial mole, extensive placental sampling is required. The usual one or two blocks taken routinely for pathological examination often prove inadequate. Cistern formation can be inconspicuous, especially in older moles, and in retrospective studies with limited numbers of histological slides, it may be difficult to demonstrate.

The trophoblastic hyperplasia of partial moles is often inconspicuous, but its magnitude presents a spectrum, with only rare cases displaying gross hyperplasia comparable with complete moles. The increased levels of hCG found in some partial mole patients may reflect an increased amount of trophoblast. Usually the hyperplasia is confined to the syncytiotrophoblast, which is vacuolized, and only a few cases show cytotrophoblastic proliferation (*70, 71*).

Triploidy occurs in 1–3% of all recognized conceptions and in about 20% of spontaneous abortions with an abnormal karyotype (*72*); not all of these become PHM. Data from studies of some species of mammal indicate that aging of eggs, either within the follicle or after ovulation, can result in an increase in the incidence of triploid conceptuses, and some data suggest the same also applies in man (*58*).

The triploid fetus usually dies at 8–9 weeks of menstrual age. In the PHM placenta the vessels collapse, the endothelium degenerates, and the erythroblasts (see Table 3) also disappear. In such cases the concomitant fibrosis of the villous mesenchyme proceeds both in the

core of the small unaffected villi and in the walls of the cisterns. This is the common picture, since early fetal death is the rule, survival beyond the first trimester an exception, and term delivery a rarity.

The morphological comparison between the two syndromes of complete and partial mole is summarized in Table 3.

The most important clinical aspect of PHM is whether or not it can give rise to choriocarcinoma. Trophoblastic hyperplasia, high hCG levels, and their often slow return to normal create a *prima facie* case, strengthened by several reports where post-evacuation hCG curves warranted chemotherapy (*68, 73, 74*). Choriocarcinoma has not been reported after unequivocal PHM, but the evidence is limited since present diagnostic and therapeutic measures for GTT infrequently yield material for the pathologist.

4.1.3 *Relative frequency of complete and partial hydatidiform mole*

The distribution of CHM and PHM depends on the method of selection of the cases to be studied. For example, in a series of spontaneous abortions, in which triploidy is common, the relative frequency of PHM was 69% (*28*). In published reports of cases diagnosed clinically as HM the percentage that are PHMs has ranged from 3% (*75*) to 25% (*66*). Thus present evidence indicates that PHM is the more common event because triploid conceptions occur relatively frequently. Aborted conceptions are rarely examined, however, and in normal clinical and pathological practice most conceptions recognized as HM prove to be CHM.

4.2 Risk factors for hydatidiform mole

Little is at present known to account for the differences in the incidence of HM in different countries, and it is evident that future studies should collect and analyse data for CHM and PHM as separate entities. In particular, it is necessary to confirm that the apparent excess of moles reported in some countries is attributable wholly or mainly to CHM.

A variety of risk factors may play a role in the causation of HM, and these will now be considered.

Table 3. Morphology of complete and partial hydatidiform moles

Embryo/fetus	Appearance of villi	Hydropic swelling: oedema to cistern formation	Vascularity of villi	Trophoblast
Complete mole (46 XX, 46 XY)				
Absent	Round to ovoid outline Delayed maturation Random mesenchymal cell necrosis during cistern formation	Pronounced All villi affected early in molar evolution	Capillaries formed *in situ*, empty of blood, disappear with cistern formation	Gross cyto- and syncytial hyperplasia of haphazard distribution unrelated to mesenchymal changes
Partial mole (triploid)				
Present (direct or indirect evidence); tends to die early	Pronounced scalloping increasing with villous fibrosis No mesenchymal cell necrosis	Distinctly focal, less pronounced and slow in evolution Slow maturation of unaffected villi Maze-like cisterns after mid-gestation in some cases	Persistent and functioning capillaries that tend to disappear late from cistern walls Often fetal (nucleated) erythroblasts Avascularity and fibrosis of villous mesenchyme after fetal death	Immaturity and focal, mild to moderate hyperplasia, mostly syncytial Trophoblastic inclusions in villous stroma in most cases

4.2.1 *Age*

The age at which a pregnancy occurs has an important influence on the risk of hydatidiform mole (*4, 5, 7–9, 12, 13, 20, 76*). The risk of HM is lowest for a pregnancy in the age group 20–35 years. The risk is slightly higher for pregnancies in those aged 15–20 years (*9, 28, 52, 77*), and is much higher, about 20-fold, for a pregnancy in girls under 15 years (*78*). There is a progressive increase in risk above 40 years of age and for women over 50 years the risk that a pregnancy will result in HM is some 200 times greater than for those 20–35 years of age (*79*).

4.2.2 *Ethnic group*

Large differences in the incidence of hydatidiform mole have been noted between various ethnic groups. In the United States of America from 1970 to 1977, hydatidiform mole was only half as frequent in black women as in other women (*8*). In Singapore from 1963 to 1965, women of Eurasian descent had a rate of hydatidiform mole twice that of Chinese, Indian, or Malaysian women (*9*). In Israel from 1955 to 1965, Jewish women over 45 years old who were born in Europe had a significantly higher incidence of hydatidiform mole than women of the same age who were born in Africa, Asia, or Israel (*13*).

Jacobs et al. (*28*) have recently produced evidence that Filipinos in Hawaii seem to maintain the high risk of hydatidiform mole that they have in their own country. However, Japanese and other East Asians originating from high-risk countries seem to have lost this risk in the Hawaiian study. This suggests that cultural factors affect the immigrants in their new environment.

4.2.3 *Obstetric history*

The independent effect of the number of pregnancies (or gravidity) on the risk of hydatidiform mole has not been adequately studied. Since gravidity and age are correlated, gravidity-specific rates of hydatidiform mole would be expected to increase with increasing gravidity. In one study (*12*), in which rates of hydatidiform mole were classified by both age and gravidity, the trend toward increasing rates with higher gravidity was evident only in the younger age groups. This effect was small and not statistically signif-

icant. Another report (*14*) has corroborated the conclusion that gravidity has no significant effect on the incidence of hydatidiform mole.

Women who have had a previous hydatidiform mole appear to be at a greatly increased risk of having another (*12, 13, 22, 75, 80*). The relative risk of developing another hydatidiform mole ranges from 20 to 40 times that for the general population in reported studies (*12, 13, 52*). It was reported to the Group that, in a group of 2977 women in the United Kingdom who had already had one HM, second moles occurred in 2.2% of 1125 subsequent pregnancies.

The risk of choriocarcinoma may be increased for term deliveries following HM, but the data are scanty and in such cases it may be difficult or impossible to determine which was the causal pregnancy.

Women who have given birth to twins may also be at an increased risk of having a hydatidiform mole. In one study (*81*), the incidence of HM among such women was significantly higher than that for the general population. Twinning and HM may be different expressions of an underlying problem with fertilization or gametogenesis.

4.2.4 *Genetic factors*

Cytogenetic studies in two series (*57, 62*) gave a frequency of balanced translocations in women with CHM of 4.6% compared with a frequency of 0.6% for normal populations (*82*). It is possible that in women carrying a balanced translocation the chance of the meiotic process being disturbed are increased so that empty or inactivated eggs may be more likely in these patients.

The ABO blood groups of the patients and their husbands have not been found to be different from those of the normal population under study (*83–85*). In one investigation (*85*) of women with hydatidiform mole in Japan, the frequency of Rh-negative individuals was significantly lower than that in the general population.

There is no acceptable published evidence for the influence of consanguinity, or family history, on the incidence of mole.

4.2.5 *Diet*

Although a dietary etiology for hydatidiform mole has been widely discussed, evidence supporting this hypothesis is weak. Early reports from China (Province of Taiwan) (*88*), Mexico (*87*), and the

Philippines (*37, 48*) speculated that the reported high incidence of hydatidiform mole among poor women might be attributable to a protein-deficient diet. One laboratory study of 25 women with HM attempted to evaluate this hypothesis (*89*); the authors observed serum creatinine and urea concentrations to be significantly increased compared with controls, and the serum albumin and total protein significantly decreased. The authors interpreted these findings as indicative of increased catabolism due to dietary inadequacies. However, whether these changes were the cause or the result of HM is unclear. Dietary histories if available might have helped to resolve this question.

Other reports have refuted the hypothesis of a dietary etiology. Two reports from Hawaii (*26, 27*) failed to show an association between HM and diet. A study of native Alaskans (*24*) decribed a high incidence of HM in a population that consumes a high-protein diet of game and fish. In another study in Mexico (*22*) food histories were obtained from women with HM and from a control group of pregnant women. No significant differences in intake of energy, carbohydrates, proteins, and fats were observed. Thus, the hypothesis of a dietary etiology of HM stems from uncontrolled clinical observations and is not supported by any of the existing data.

4.3 Diagnosis and evacuation of hydatidiform mole

These aspects are well known to obstetricians and need not be considered in detail here. Diagnosis depends on clinical suspicion arising from excessive nausea, vomiting, malaise, pre-eclampsia occurring early, uterus large for gestational age, passage of vesicles, or uterine bleeding of any degree. Ultrasonography is a useful diagnostic aid for both CHM and PHM. The values of hCG may be in the normal pregnancy range and may be elevated to more than 100 000 IU/litre but in only about 25% of HM patients. While some or all of the above signs may be present in both CHM and PHM the latter may more frequently present as a missed or incomplete abortion.

Several methods of evacuation are available and the one chosen may be determined largely by local and individual circumstances. Although hysterectomy and hysterotomy may appear to be the most effective ways of removing all mole tissue, the evidence reviewed below (section 4.5.3) suggests that they may carry a greater risk of sequelae. The available evidence suggests that evacuation by con-

traction of the uterus when labour has been induced by oxytocin or prostaglandins may also lead to greater dissemination than evacuation by vacuum or conventional curettage (*76*). Ecbolic agents used at the time of uterine aspiration may be acceptable, but more data are required. The Group felt that vacuum aspiration is the preferred method for evacuating the uterus. In addition, it was recommended that all women with HM should have a chest X-ray at the time of evacuation as a basis for the evaluation of possible sequelae.

4.4 Risks resulting from hydatidiform mole

In trying to assess the magnitude of the risks associated with HM it is necessary to consider factors that are intrinsic to the mole itself as well as factors resulting from the influence of different methods of management. From the patient's point of view, HM is significant primarily as a failed pregnancy. CHM may, however, be accompanied by excessive nausea and vomiting, by pre-eclampsia, vascular coagulopathies, significant blood loss, and other complications listed below. These complications, and the methods used for the evacuation of mole, fall within general obstetric practice and they are not our concern here, except in so far as they may influence general health and prognosis. It should be noted that for women of poor nutritional status and those with chronic disease states, the occurrence of CHM even with no sequelae may constitute a significant threat to general health over and above that associated, for instance, with spontaneous abortion.

Since the prognosis of patients with PHM is not yet well defined, it seems appropriate that they should be followed up in the same way as for CHM.

The patient with hydatidiform mole is exposed to several risks. There is the risk of morbidity or death from uterine haemorrhage, coagulopathy, uterine perforation, trophoblastic embolism, or infection. There are also the risks of loss of reproductive function and of the associated surgery if a hysterectomy is performed. Subsequently, there is the risk of a further mole or impaired obstetric performance and the risk of developing GTT.

In some developing countries early loss of reproductive function has serious social consequences for the patient. Also, haemorrhage due to HM or IM in a patient already anaemic or malnourished may have consequences that would be rapidly corrected in an advanced

society but which may be disastrous in the absence of transfusion facilities. Up to 60% of HM patients in developed countries need transfusions.

4.5 Prognostic factors for development of gestational trophoblastic tumour following hydatidiform mole

The principal long-term risk to the mole patient is that of continued trophoblastic activity either as invasive mole or choriocarcinoma, and we may consider here the possibility that the risk of these sequelae can be ascertained prior to or immediately after evacuation of a mole.

On the basis of published morphological data, the risk of choriocarcinoma after HM in the pre-chemotherapy era was estimated to be less than 3%, and it probably never exceeds 5% (*52*). Assessment of the risk of invasive mole depends on the criteria adopted for its identification, but about 90% resolve spontaneously.

A number of different factors have been generally regarded as being associated with an increased risk of developing GTT. Many of these have been poorly documented and are anecdotal in nature. Those that appear to be the best documented are uterine size and pre-evacuation hCG level.

4.5.1 *Uterine size and pre-evacuation hCG level*

The large-for-dates uterus with bilateral ovarian enlargement has been reported to carry a high risk of sequelae requiring therapy (*90, 91*). Large-for-dates uteri appear to have a strong correlation with pre-eclampsia (*52, 90, 92*), but it is unlikely that pre-eclampsia is an additional risk factor in itself, since it is reflected in uterine size and in hCG values.

Some groups use a pre-evacuation hCG level of more than 100 000 IU/litre as a factor to distinguish women at higher risk of sequelae (*93*). High hCG levels also tend to be associated with large uteri. In a reported series in the United Kingdom, 6 out of 26 individuals with pre-evacuation values of more than 100 000 IU/litre in urine or serum required chemotherapy, and 4 out of 72 individuals with values of less than 100 000 IU/litre required treatment (*78*).

Other factors that are not well documented but which increase the risk of GTT are listed below.

4.5.2 *Other risk factors*

An influential report in the 1940s (*25*) indicated a good correlation between *trophoblastic hyperplasia* in moles and malignant sequelae. Another authority later stated "the mere fact of a patient's having harboured a hydatidiform mole is, of itself, of far greater prognostic significance than any histological minutiae it may show" (*53*). No relationship between the histological grade of a hydatidiform mole and subsequent malignancy was found in later studies (*91, 94–96*).

Patients with *repeated mole* may be more at risk of sequelae but the numbers are too small to be reliably assessed. A study in the USA (*90*) found fewer patients with post-mole trophoblastic tumours where the *gestation time* had been less than 10 weeks, but in a study in the United Kingdom (*76*) a higher incidence was found with gestation times of less than 15 weeks.

Thyrotoxic features have also been regarded as high-risk factors, but hyperthyroidism in mole patients is rare, although increased thyroid function may be detected biochemically (*97*). Hyperthyroidism in HM and choriocarcinoma patients is thought to be related to high hCG levels (*98, 99*).

Parity has not been clearly identified as a factor increasing the risk of sequelae. In an Asian population the risk was greater with later pregnancies (*9*). In a European population the first pregnancy was most at risk (*52*).

Transplantation of trophoblastic syncytium to the lungs is a feature of normal pregnancy and it may be excessive in moles. Massive trophoblastic embolism has been listed as an indication for chemotherapy (*93*), but it seems that treatment is needed to lyse transported trophoblast rather than because of an increased risk of GTT sequelae. Both trophoblastic embolization and *disseminated intravascular coagulation,* another proposed prognostic factor for treatable sequelae, occur almost exclusively with large-for-dates uteri and high hCG levels.

Metastases at the time HM is evacuated may undergo spontaneous regression (*100–102*). None the less, some workers regard them as an indication for chemotherapeutic intervention. Metastases in the lungs or vagina are not necessarily an indication of progressive disease and those detected in the first 2–3 months after evacuation of a mole may have no more significance than those present at the time of evacuation. This cannot be taken for granted, however, and

correlation with hCG values is essential; progressively falling values of hCG indicate that resolution of these lesions will probably occur spontaneously, but increasing values are a strong indication for intervention.

Multiple curettages are frequently performed after molar evacuation to reduce the risk of persistent disease. But, there are no data to indicate that this is advantageous.

4.5.3 *Method of primary treatment*

The effect of the mode of evacuation of HM on sequelae is clearly an important question, but data are available from only a few studies. In a series of 611 patients the probability of requiring chemotherapy by the criteria applied at that centre was about 2.5 times greater in those who underwent hysterectomy, hysterotomy, or medical induction with oxytocin or prostaglandins than it was in those having spontaneous evacuation, vacuum aspiration, or curettage only (*76*). In another study, Curry et al. (*90*) observed that hysterotomy appeared to increase the incidence of GTT and noted the highest incidence of GTT in patients undergoing hysterectomy. However, selection for hysterotomy or hysterectomy may be influenced by age and uterine size.

In a longitudinal study of 868 cases admitted to a maternity hospital in Manila the incidence of IM and choriocarcinoma was found to be 38 out of 244 (15.9%) in those having prophylactic hysterectomy and 4 out of 624 (6.6%) in the non-hysterectomized follow-up cases (*103*). This difference was attributed to an increased risk of malignancy in the older age group, but when it was age-corrected there was still a higher incidence in the hysterectomy group.

4.5.4 *Steroids and oral contraception*

It has been reported that patients who were given steroid sex hormones or combination oral contraceptive pills in the period between the evacuation of HM and fall of hCG to undetectable levels, required treatment for IM or CC in 24.6% of cases compared with 8.8% in those not taking any steroids (*76*). There was no evidence of any effect from steroids taken after hCG had become undetectable.

Other centres do not appear to have encountered this problem and routine use of oral contraceptives following mole is standard practice in the USA (*93*). However, different methods of selection of patients for chemotherapy after mole would tend to obscure the effects of steroids and more data are therefore required.

4.6 Follow-up after hydatidiform mole and hCG assay

The purpose of following up patients after HM is to detect any continued trophoblastic activity and to provide a basis for therapeutic intervention. Continued trophoblastic activity is detected by finding hCG in serum or urine, but it is necessary to take into account the metabolic and renal clearance of hCG. This clearance proceeds at about 1 ml/min and it requires 10–20 days for hCG to become undetectable (i.e., less than 5 IU/litre) after a normal pregnancy. The time taken to reach the normal level is influenced by the initial pre-evacuation level of hCG and the clearance rate. Finding hCG more than 20 days after delivery indicates continued secretion of hCG by trophoblastic tissue (*104, 105*). After a non-molar abortion, hCG may take a few days longer to become undetectable because of a higher initial starting value in early pregnancy and possibly because of retained products of conception. As a rough guide, the 24-hour hCG excretion rate in urine is about 1.5 times greater than the corresponding serum concentration per litre. (The hCG content of random urine specimens shows a less consistent relation to the serum concentrations.)

Continued detection of hCG may be due to retained mole in the uterine cavity, but if this has been satisfactorily cleared by curettage then it is probable that trophoblast is active in the uterine wall or at sites to which trophoblast has been deported.

Trophoblast that has not undergone malignant transformation to choriocarcinoma rarely survives beyond 300 days after conception and retained mole tissue usually tends to die much earlier. After evacuation of HM, the level of hCG may fall as rapidly as after a non-molar abortion, but it is evident that if the initial hCG concentration in the body fluids is very high, it will take longer to become undetectable. In any case, it is the underlying trend in hCG values that is important. In all patients there is an initial fall in hCG values following evacuation, but the rate of decline is variable thereafter.

Radioimmunoassay has proved to be the most consistent method for sensitive hCG assays although a similar degree of reliability may

be obtained using immunoenzymic or immunofluorescent methods. A minimum sensitivity of 5 IU/litre in serum is desirable and the assay procedure should not take more than 24 hours. Haemagglutination-inhibition methods are less sensitive. Standardization of reagents for use in trophoblastic tumour treatment centres would be advantageous. It should be noted that the existing assay technology still falls short of that desirable for worldwide use. Consideration needs to be given to the development of assay techniques suitable for use in developing countries. Immunoassay values should be quoted in terms of the First International Reference Preparation for Chorionic Gonadotrophin, Human, for Immunoassay (*106*).

The feasibility of a follow-up service for HM patients on a national scale has been demonstrated in the United Kingdom since 1972, and the following observations are based on this and earlier studies (*52, 104*).

In most cases there is a progressive fall in hCG values following evacuation of HM indicating a continued regression of residual trophoblast, although it may take 4 months or more for hCG levels to reach the limit of detection. In others there may be temporary increases in hCG values followed by a decline, the limit of detection being reached spontaneously in 90% of cases.

It has been observed that persisting high values of hCG in serum or urine (25 000 IU/litre) more than 4 weeks after evacuation indicate a continued high level of trophoblastic activity (*107*). This may be due to choriocarcinoma, but is more usually due to invasive mole in the uterine wall and it is often associated with theca-lutein cysts. These patients are at risk of uterine perforation and require close observation or intervention with chemotherapy.

For patients with HM it is recommended that tests for hCG should be continued for at least 6 months after hCG has become undetectable. Late recrudescence can occur as long as 24 months post-evacuation, but this is rare.

Ideally, tests for hCG should be performed every 2 weeks until the limit of detection is reached, after which tests may be continued monthly until one year after evacuation and then every 3 months in the second year of follow-up. However, when the patient wishes to proceed with another pregnancy, confirmation that hCG levels have been normal for 6 months provides a reasonable safeguard.

It is clear that cases of hydropic change carry little risk of late sequelae and do not need a follow-up procedure. In cases where the diagnosis of hydropic change or HM is in doubt, short-term follow-

up to confirm that hCG has become undetectable in 3 consecutive assays at monthly intervals is probably adequate. In addition to follow-up by hCG, some HM patients may require a further chest X-ray depending on the level and trend of the hCG values.

4.7 Timing of therapeutic intervention

It is recognized that for the 2–3% of patients who develop potentially fatal choriocarcinoma from CHM it is desirable to start chemotherapy at an early stage, since the longer the interval between evacuation and chemotherapy the greater the risk of late drug resistance (*52, 108, 109*). However, it is probably undesirable that this risk, which with optimal chemotherapy is quite small, should lead to the treatment of a large number of patients with invasive mole who would undergo spontaneous regression.

4.8 Prophylactic chemotherapy for patients with hydatidiform mole

Shortly after the introduction of chemotherapy for trophoblastic tumours it was proposed that this treatment would be more effective in preventing post-mole choriocarcinoma if given at the time of, or soon after, evacuation of the mole. This would be a powerful argument if chemotherapy were effective and harmless, especially in countries where reliable follow-up is difficult, but unfortunately, there are serious difficulties. It has been proposed by some that prophylactic chemotherapy should be given to all patients with mole, while others believe that they can reliably predict the patients at high risk of sequelae and give prophylaxis to these patients only.

Methotrexate was used in the Philippines and Japan in the 1960s (*110–113*). Although some authors felt that the case for prophylactic therapy was established, follow-up studies were generally of a limited duration. It also became clear that dose schedules that were safe for all patients failed to prevent choriocarcinoma.

Deaths from prophylactic chemotherapy have rarely been reported. In Singapore (*114*) 4.5% of patients receiving three courses (150 mg total dose) of methotrexate required subsequent chemotherapy compared with 8.7% in untreated controls, but the mortality rate in the prophylactic group was 2.2% compared with 0.5% in controls. In Italy, 9% of 250 patients who did not receive prophylactic chemotherapy subsequently required chemotherapy compared with 3% of 104 patients who did receive prophylactic treatment (*115*).

One group has defined high-risk and low-risk moles in the context of probable local or metastatic sequelae as discussed above (*116*). Patients with high-risk features were treated with dactinomycin (actinomycin D). A single course of dactinomycin given as prophylactic therapy reduced the incidence of GTT requiring further chemotherapy to 3.6/100 mole patients. A single 5-day course of dactinomycin may be expected to reduce some of the morbidity and to eliminate the most susceptible lesions following HM at the cost of modest toxic effects, including some alopecia. A drug dependent on renal excretion, such as methotrexate, is particularly hazardous for prophylactic use and although the risk may be reduced by sequential use of calcium folinate (folinic acid), this is a relatively expensive drug combination. Dactinomycin is probably the drug of choice on grounds of effectiveness and low cost.

The question whether the prophylactic use of cytotoxic agents for HM increases the risk of late drug resistance is not resolved by present evidence. In view of this and the other hazards of cytotoxic chemotherapy, no general recommendation for prophylactic treatment can be made at this time. There is, however, a need to determine by appropriate studies the possible value of such treatment.

4.9 Recommendations for research

In view of the unresolved issue of the value or otherwise of prophylactic chemotherapy, a careful randomized clinical trial should be done with an adequate follow-up period to evaluate the efficacy of prophylactic chemotherapy in preventing GTT after evacuation of a HM.

5. INVASIVE MOLE AND CHORIOCARCINOMA

5.1 Invasive mole

Invasive mole (IM) is hydatidiform mole that has penetrated deeply into the uterine wall or has produced metastases, or both. It is recognized primarily as a sequel to the evacuation of HM, the majority of cases being recognized within 6 months. It may cause haemorrhage from vaginal metastases or from the uterus and it may perforate the uterine wall. Theca-lutein cysts may be prominent and IM may also produce a small number of metastatic shadows up to 2 cm in diameter on the chest X-ray. Rarely, metastases have been

recorded at other sites, including the brain. Microscopically IM is characterized by hyperplasia of both cytotrophoblastic and syncytial elements and persistence of villous structures both in uterine and metastatic lesions (*53*). It is rarely fatal, and is in most instances a self-limiting process, but therapeutic intervention may be necessary either to prevent, or because of, uterine haemorrhage or perforation, or because of the difficulty of distinguishing IM from choriocarcinoma by clinical methods. A review of the British and American literature from 1950 to 1960 indicated that 3.4% of documented cases of IM subsequently died from histologically verified choriocarcinoma (*117*).

5.2 Placental site trophoblastic tumour

In 1976 "trophoblastic pseudotumour of the uterus" was proposed as the name of a lesion that consisted of an exaggerated tendency of trophoblastic cells at the implantation site to infiltrate the endometrium and myometrium (*118*). It was suggested that many such cases had previously been diagnosed as choriocarcinoma, leiomyosarcoma, uterine sarcoma, mixed mesodermal tumour, or malignant mesenchymal tumour. Since then more cases have been described and associated with earlier designations of the lesion as chorioma, syncytioma, atypical choriocarcinoma, chorionepitheliosis, and exaggerated placental site reaction.

Subsequently the name placental site trophoblastic tumour (PSTT) was proposed (*119*). It is a rare condition and nearly all reported cases have followed term pregnancies or non-molar abortions. Its trophoblastic nature is confirmed by the cellular morphology, which is predominantly cytotrophoblastic, and by the histochemical identification of hCG producing cells. It is distinguished from choriocarcinoma by the paucity of multinucleated syncytial cells, which probably accounts for the fact that it is associated with a relatively low level of hCG production. It has been accompanied in two instances by a nephrotic-like syndrome and although it is not insensitive to cytotoxic therapy, eradication may prove difficult. If it is confined to the uterus, as is usually the case, it can be satisfactorily treated by hysterectomy. When it extends beyond the uterus and the reach of surgery, it may prove fatal (*120*). The full clinical spectrum of this tumour has yet to be defined and there may be difficulty in distinguishing it from ectopic hCG-producing carcinomas originating in other tissues.

5.3 Choriocarcinoma

The histopathological and clinical features of this cancer are too well described to merit repetition here, but it may be appropriate to refer to some aspects. Choriocarcinoma (CC) is distinguished morphologically from IM mainly by its lack of villous structures. The characteristic lesion is a core of pleomorphic cytotrophoblast surrounded by a rim of syncytium with extensive areas of haemorrhage. Choriocarcinoma can follow normal pregnancy, non-molar abortion, ectopic pregnancy, or hydatidiform mole. Cases following term delivery or non-molar abortion tend to be diagnosed at a more advanced stage because the index of suspicion is at a lower level and because the follow-up facilities following HM do not apply. It is indeed possible that many cases of choriocarcinoma are missed. Some cause intracranial haemorrhage, gastrointestinal tract bleeding, or acute pulmonary symptoms and are unlikely to be recognized as due to choriocarcinoma unless a meticulous autopsy is performed.

Nevertheless, the main diagnostic problem arises in cases after HM since to obtain histological proof of choriocarcinoma from curettings is very unusual.

5.4 Risk-factors for choriocarcinoma

5.4.1 *Age*

The median age for women with choriocarcinoma is generally somewhat higher than the median age for pregnancy. Some reports (*43, 45*) describe slightly higher rates of choriocarcinoma for teenagers than for women aged 20–40 years, while others (*4, 11, 44*) have noted lower rates. As with hydatidiform mole, women aged 40 years and older account for a minority of cases of choriocarcinoma owing to their low fertility. The potential effect of the age of the father is unknown.

5.4.2 *Ethnic group*

The Group considered that the data relating to the incidence of GTT in different ethnic groups are inadequate and that no conclusions could be drawn.

5.4.3 *Obstetric history*

The data concerning the effect of the number of pregnancies independent of age are inadequate and no conclusion can therefore be drawn.

Bad obstetric histories with increased fetal wastage have been reported in association with GTT (*49, 121*). It was found (*49*) that the risk of GTT was 21, 32, and 34 times higher, respectively, for women with 1, 2, or 3 or more fetal losses than those whose known pregnancies all ended in live births. The marked effect of one fetal loss in this study resulted from scoring an antecedent HM as a fetal loss.

5.4.4 *Antecedent pregnancy*

In Caucasian populations term deliveries, non-molar abortions, and hydatidiform mole contribute roughly equal numbers of cases of choriocarcinoma although there may slightly more cases following HM. The majority of cases of choriocarcinoma follow abnormal pregnancies (Table 4). The higher proportion of choriocarcinoma following HM could be attributable either to the high incidence of HM in some countries or to a higher percentage of HM patients in those countries developing choriocarcinoma. The percentage of cases of choriocarcinoma preceded by HM ranges from 29% (*15, 49*) to 83% (*45*) in reports published since 1960. Since HM is an uncommon pregnancy outcome, the high percentage of cases of choriocarcinoma that follow HM indicates that HM is a powerful risk factor for choriocarcinoma. One review (*14*) reported that the risk of a woman with HM developing choriocarcinoma ranged from 2% to 19% in different studies, although it is doubtful if it ever exceeds 5% (*122*). Overall, the risk of choriocarcinoma after HM is about 1000 times higher than that after a normal-term delivery (*104*).

5.4.5 *Genetic factors in choriocarcinoma*

When gestational choriocarcinoma follows a normal-term birth, then the products of conception from which the malignancy arises are assumed to be diploid and heterozygous with a haploid genetic contribution from each parent. In a series of cases collected in the United Kingdom and reported to the Group, pregnancies preceding

Table 4. Percentage distribution of antecedents of choriocarcinoma in selected studies by region

	Country or territory	Reference	Period of study	No. of cases	Hydatidiform mole	Birth	Abortion and ectopic pregnancy	Unknown
Africa	South Africa	(*123*)	1968–77	24	33	25	42	—
	Uganda	(*124*)	1965–68	35	54	14	32	—
	Uganda	(*19*)	1967–70	26	50	15	35	—
Asia	China (Province of Taiwan)[a]	(*30*)	1951–60	24	54	17	29	—
	China (Province of Taiwan)[a]	(*88*)	1955–62	22	82	5	14	—
	Hong Kong[a]	(*2*)	1953–61	41	44	24	31	—
	Israel[a]	(*14*)	1950–65	32	41	34	19	6
	Japan	(*125*)	1960–62	102	56	9	34	—
	Singapore	(*45*)	1960–70	122	83	6	11	1
	Philippines	(*48*)	1950–62	105	60	11	23	6
	Philippines	(*49*)	1970–74	73	29	26	45	—
Europe	Denmark[a]	(*126*)	1940–69	48	42	38	21	—
	England[a]	(*109*)	1958–73	101	34	37	30	
	Norway[a]	(*15*)	1932–61	34	29	35	35	—

[a] Choriocarcinoma diagnosed by histology.

the tumours resulted in the birth of approximately equal numbers of female and male children.

Thus in choriocarcinoma a malignancy can arise in the case of complete mole from an androgenetic diploid conceptus (most often this will be female and homozygous, but more rarely may be male and heterozygous) or from a normal diploid conceptus of either sex. The possibility of origin from a triploid conceptus has yet to be proved. When choriocarcinoma follows an abortion, it is difficult to be sure of the genetic origin of the tumour if the products of conception have not been adequately examined. Cytogenetic studies of choriocarcinoma are hampered by the lack of fresh tumour tissue for culture *in vitro*. The available data are too few for conclusions to be drawn (*127, 128*).

There are no data suitable for analysis on the effects of consanguinity on the incidence of choriocarcinoma or on its possible prognostic effects.

(1) *ABO blood group*. Data from the USA (*129*), the United Kingdom (*83, 109*), and Singapore (*84*) for patients with choriocarcinoma showed a slight excess in Group A and a deficit in Group O. The data from the United Kingdom suggested that the risk of a woman developing choriocarcinoma is also influenced by the blood group of her husband and this effect was most marked in cases where choriocarcinoma was preceded by a term delivery (*83*). In a population in which the frequency of blood groups A and O are approximately equal it would be expected that the ratio of the sum of incompatible matings to the sum of compatible matings would be unity.

$$\text{Thus, } \frac{A \times O + O \times A}{A \times A + O \times O} = 1.$$

At Charing Cross Hospital, London, in a series of 115 patients with choriocarcinoma following term pregnancy or non-molar abortion for whom mating types were available, this ratio of incompatible/compatible matings was 2.19, indicating a predisposition to choriocarcinoma in the incompatible matings (*130*). Because of the limited data it is important that future studies should include blood group data on both partners.

(2) *HLA types*. There are no published data on the HLA types of a series of patients and husbands ascertained at the time of evacuation of HM. Data are, however, available on patients and

husbands in a series treated for GTT (*131*). The patients were divided into low-, medium-, and high-risk categories according to a scoring system (*109*). The overall frequencies of the HLA-A and HLA-B locus antigens in 225 Caucasian patients did not differ significantly from those of the normal control population. However, the degree of incompatibility between husband and wife, as measured by the number of antigenic incompatibilities (0, 1, or 2), indicated that there is a trend in patients who are *more* compatible with their husbands for the B locus antigens to fall into one of the two higher-risk categories. Again, because of the limited data more studies are needed.

In the cases in which choriocarcinoma is preceded by the birth of a viable infant, the child and tumour are presumed to be isogenic. A child can be incompatible with the mother for one allele at each HLA locus. Scoring the number of incompatibilities is straightforward but there may be uncertainties owing to the presence of undefined specificities or apparent homozygosity. Data were available on 39 mother–child pairs; the majority (67%) of offspring were incompatible with the mother at both the A and B loci, and 8% were found to be compatible at both loci. In the United Kingdom, about 2% of offspring are expected to be compatible with the mother at both the A and B loci; thus there is a small excess of compatible fetuses among the patients. Although the data showed that, in the majority of cases, choriocarcinoma arises after an HLA incompatible fetus, the small excess of compatible fetuses is of interest. A similar trend has been observed in the USA by Lewis & Terasaki (*132*). Since most of the patients who develop a choriocarcinoma following a live-term birth are in the high-risk prognostic group, the excess of compatible fetuses tends to support the idea that these patients are more compatibly mated on the HLA system than those in other risk categories (*131*).

5.5 Immune response to HLA antigens in gestational trophoblastic tumour

In relation to the immunogenetic properties of a molar conception, there is evidence that among patients requiring treatment, the mole was immunogenic. HLA antibodies against paternal antigen have been detected in 14 out of 34 cases in which a mole was the only recorded pregnancy and no blood transfusions had been given. Furthermore these molar first pregnancies were more immunogenic

than normal ones, 41% of patients with a single molar pregnancy being immunized, against an expectation of 20% for normal first pregnancies (*79*). Immunization cannot be attributed to fetal lymphocytes in the case of classical mole, so either the trophoblast or the villous stroma is the source of the immunogen. Antigenic sites are so sparse that they cannot be detected by histochemical tests on the trophoblast, but it is possible that sufficient antigen is produced to act as an immunogen.

Genes in the HLA region control the immune response for any particular set of antigens so it is possible to classify people as responders and non-responders. For the HLA system, using the prognostic scoring system (*109*), the patients in the high-risk group were more likely to form antibody than those in the lower-risk group (*131*). This observation held even when allowance was made for various stimuli to produce antibody, i.e., number of pregnancies and transfusions, that each patient received. It has been suggested that the presence of HLA antibodies in the high-risk group could have an enhancing effect on the tumour (*131*).

5.6 Recommendations for research

The group formulated the following recommendations for research on the genetics of gestational trophoblastic tumours (GTT), in order of priority.

(1) A genetic study of histologically defined hydatidiform moles (HM) should be made by determining the karyotype, including chromosomal polymorphisms, of the molar tissue and also that of the patient and her partner/husband. Determination of biochemical polymorphisms is also desirable. Patients in this study should be followed up in order to correlate the genetics of the HM with subsequent developments.

(2) Every effort should be made to obtain information on the karyotypes of choriocarcinoma by studying the tumours removed by surgery. Examination of the karyotypes (including chromosomal polymorphisms) of the patient and her partner/husband are essential in cases of GTT following a live birth; the antecedent child's karyotype should also be determined. In order to obtain *in vitro* growth of choriocarcinoma cells it may be necessary to make xenografts. The establishment of choriocarcinoma cell lines from such xenografts would be important for research on the characteristics of these cells.

(3a) The ABO and if possible the HLA types of the patient and her partner/husband should be determined in cases of HM and GTT following any type of pregnancy. When GTT follows a live-birth, the antecedent child should also be typed. This would give information on the influence of ABO and HLA on the incidence and prognosis in GTT.

(3b) The serum of patients with HM and GTT could be examined for the presence of HLA antibodies in order to study the immune response of the patient to HLA antigens.

6. CASE SELECTION FOR ACTIVE TREATMENT: RISKS AND PROGNOSTIC FACTORS

It is necessary to recognize that the various criteria and policies that are applied in different centres have an important effect on what constitutes a series of patients treated for trophoblastic tumours.

It would be ideal if in most instances a morphological diagnosis were obtained as is standard practice for virtually all other cancers. The disadvantage of such a policy is that it would generally require laparotomy, often with hysterectomy, and in about 10–15% of cases might, in addition, require thoracotomy. Since the detection of hCG narrows the possibilities to a trophoblastic tumour and given that delay in initiating treatment may be disadvantageous—for instance, because of the development of brain metastases—there is a strong incentive to rely on clinical criteria. Moreover, a possible, unnecessary loss of reproductive function is often too high a price to pay for a histological diagnosis.

Some centres have adopted a simple policy of giving chemotherapy to any patient in whom hCG is detectable at a specified level at a defined time such as 8 weeks after evacuation (*90, 133*). The proportion of patients treated under such a policy is usually about 20–25% of all mole patients. This proportion depends on the sensitivity of the hCG assay used, and in one study using a urinary radioimmunoassay, almost 50% of the 458 cases studied still had detectable levels of hCG 8 weeks after evacuation (*104*).

By using strictly defined criteria similar to those set out below and including a longer period before intervention because of raised hCG values (*76, 115*), it has been found that 6–10% of HM patients

require chemotherapy. In the remainder, spontaneous regression of the trophoblast occurred and it may be argued that the proportion of HM patients exposed to potentially dangerous and mutagenic cytotoxic agents should not exceed this level. On the other hand, arguments for treating a higher proportion of HM patients with cytotoxic agents are (*a*) follow-up arrangements may be difficult to sustain, (*b*) early treatment shortens the waiting period, (*c*) early treatment may shorten the duration of treatment.

6.1 Criteria for active therapy after hydatidiform mole

The Group agreed on the following criteria for chemotherapy after HM, recognizing that these criteria have been applied in a number of centres since 1972.

- High levels of hCG more than 4 weeks after evacuation (serum level greater than 20 000 IU/litre: urine level greater than 30 000 IU/litre). This group of patients are at risk of uterine perforation by invasive mole or choriocarcinoma.
- Progressively increasing hCG values at any time after evacuation (minimum of 3 values in one month).
- Histological evidence of choriocarcinoma at any site or evidence of CNS, renal, hepatic, or gastrointestinal metastases, or pulmonary metastases greater than 2 cm in diameter or more than 3 in number.

The Group recognized that different policies are adopted with respect to persisting hCG levels and small pulmonary or vaginal metastases. Some centres intervene with chemotherapy at an early stage when hCG levels are not falling. Other centres wait for 4–6 months before intervening, in order to minimize the number of patients receiving chemotherapy.

Whereas some centres give chemotherapy to any patient with small pulmonary or vaginal metastases, others withold treatment if hCG values are observed to be falling.

6.2 Choriocarcinoma following term delivery or non-molar abortion

Trophoblastic activity detected a month or more after the end of a normal pregnancy, or an aborted conception that did not show molar change, is likely to be due to choriocarcinoma or much less

commonly to placental site tumour, and both are an indication for active treatment. Placental site tumour is considered separately, although in the absence of an adequate specimen of tissue for histological examination the distinction may not be made. In general, the factors affecting prognosis following term delivery or non-molar abortions have not been distinguished from those of choriocarcinoma following hydatidiform mole even though the genetic constitution of these tumours differs.

6.3 Risks associated with gestational trophoblastic tumour

- Death early in the course of the disease from initial extent of disease (CC only), haemorrhage, or uterine perforation.
- Death at any stage from a complication of treatment, such as infection or reactivation of heptatitis.
- Death late in the course of the disease because of resistance to all cytotoxic drugs (CC only).
- Metastases in the central nervous system and loss of neurological function (very rare in IM).
- Loss of reproductive or other function.
- Late consequences of therapy to patient or to children from subsequent pregnancies.

As chemotherapeutic methods have improved, the major risk factor that has emerged in recent years in specialized centres is that of late death as a result of drug-resistance, and coupled with this is the risk of brain metastases. It has been found that the risk of developing cytotoxic drug-resistance is related both to prognostic factors and to the way in which the patient is managed from the beginning of treatment. The risks a patient faces are therefore a function of both the disease status and the clinical management. Where the risk of developing general cytotoxic drug-resistance is low, simple and safe chemotherapy can be given. Where the risk of general cytotoxic drug-resistance is increased, more complex and hazardous methods are required from the outset. The assessment of the probability that a tumour will become drug-resistant is, therefore, a first crucial step in the correct management of the patient; this is likely to require specialized evaluation.

6.4 Prognostic factors

Since trophoblastic tumours span a broad range of pathological processes it is necessary to use all available information to predict the likely therapeutic requirements and outcome. Prognostic or risk factors can be used to classify patients into different categories for treatment, and there is evidence, or assertion, relating to a wide range of factors influencing prognosis. In attempting to assess the contribution of each of these to the final outcome, it is clear that a more or less consistent treatment policy has to be pursued for a substantial number of patients.

It became evident from studies in the 1960s that patients with trophoblastic tumours who had high hCG levels at the start of treatment, patients with a long history of symptoms or a long interval between antecedent pregnancy and the start of chemotherapy, or those who had brain or liver metastases often failed to achieve remission (*52, 108*). Later, as the choice of chemotherapeutic agents and protocols became wider, the interaction of prognostic factors with treatment protocols received attention (*109, 134, 135*).

A major limitation of the data available is that therapeutic methods have tended to evolve and more rigorous treatment has been applied where the disease appeared more advanced. Also since the early 1970s, treatment has been adjusted in many centres according to prognostic factors identified up to that time. Moreover, much of the data for analysis of prognostic factors in patients requiring chemotherapy comes from a single series.

6.4.1 *Age*

No influence of age on the response to therapy was found in one series (*90*). In another (*109*) prognosis was less favourable in older patients (more than 39 years old) than in younger patients, but the difference was not statistically significant.

6.4.2 *Ethnicity*

There are no significant data available relating ethnicity to prognosis.

6.4.3 *Number of pregnancies*

No significant effect of the number of pregnancies independent of age has been observed.

6.4.4 *Nutritional status*

Most patients with trophoblastic tumours requiring chemotherapy in Western countries are in a good nutritional state and weight loss is not common. Malnutrition as a factor in response to therapy has not been recorded. Profound anorexia is a rare factor that may complicate therapy but cannot be considered as a prognostic factor.

6.4.5 *Intercurrent disease*

No significant disease associations have been reported in any series, although earlier reports from the Philippines stated that tuberculosis was common. Active or latent viral hepatitis may be a hazard in patients undergoing chemotherapy (*136*).

6.4.6 *ABO blood groups*

As far as prognosis following treatment is concerned, the mortality rate for patients who were incompatibly mated, i.e., (A × O, O × A) was less favourable than in those who were compatibly mated (A × A, O × O). Patients with blood groups B or AB, of low frequency in some countries, had a relatively poor prognosis, whereas patients with husbands of groups B or AB tend to have a good prognosis (*130*). A similar effect of ABO groups has not been observed in the United States of America (*133*), but no comment can be made since the data have not been published. *Obviously more data are required on the ABO groups of patients and husbands throughout the world.* Centres where retrospective data are available should be encouraged to publish their results.

6.4.7 *Tumour markers*

The concentration of hCG in the body fluids at the time of starting treatment for GTT is recognized to be a major prognostic factor. There is no adequate evidence at present that specific pregnancy protein SP_1, alpha subunit, or any other biochemical tumour marker provides additional prognostic evidence.

hCG values are thought to reflect the total body burden of viable tumour in these patients. Although formal correlates have not been presented it is generally found that high hCG values are associated

with large and multiple tumours, and small amounts of hCG with small tumours. However, there are exceptions to these generalizations:

(a) It is important not to confuse the high hCG levels associated with hydatidiform mole *in utero* or immediately after evacuation with those of GTT.

(b) Some choriocarcinomas and placental site tumours produce comparatively low levels of hCG.

The importance of understanding hCG clearance and half-life in interpreting hCG results has already been emphasized. Estimates of hCG values differ substantially between different assay systems.

Some groups (*137, 138*) have taken a cut-off of 100 000 IU/litre as the demarcation between high- and low-risk patients. There is evidence that the effect of hCG values increases progressively as illustrated in Table 5 (*109*).

Table 5. Case-fatality rates for gestational trophoblastic tumour by initial urine excretion of hCG per 24 hours

Excretion of hCG in urine per 24 hours	No of deaths	No. of cases	Case-fatality rate[a]	Relative risk[b]
≤9999	4	99	4.0	1.0
10 000–99 999	17	115	14.8	3.7
100 000–999 999	22	80	27.5	6.9
>1 000 000	14	23	60.9	15.2
Total	57	317	18.0	

[a] Deaths per 100 cases.
[b] Based on an index rate for ≤9999 IU/litre of 4.0 deaths per 100 cases.
Source: reference *109*.

6.4.8 *Interval between end of antecedent pregnancy and start of chemotherapy*

The length of this interval could also be a correlate of tumour burden. However, it appears to be totally or at least partially independent of hCG values. Again, some groups have adopted a single cut-off point and patients for whom more than 4 months have elapsed between the end of the antecedent pregnancy and the start of chemotherapy are classified as high-risk (*137, 139*). Other data (*109*) showed that increasing the pregnancy–treatment interval was associated with a progressive increase in the proportion of deaths (Table 6).

Table 6. Case-fatality rates for gestational trophoblastic tumour by time interval from termination of prior pregnancy to start of chemotherapy

Time interval in completed months	No. of deaths	No. of cases	Case-fatality rate[a]	Relative risk[b]
<4	4	129	3.1	1.0
4–6	6	77	7.8	2.5
7–12	15	55	27.3	8.8
13–24	15	29	51.7	16.7
≥25	17	27	63.0	20.3
Total	57	317	18.0	

[a] Deaths per 100 cases.
[b] Based on an index rate for <4 months of 3.1 deaths per 100 cases.
Source: reference *109*.

When classified by hCG levels, the same effect of an increasing proportion of deaths with time interval was found. The interval between the end of the antecedent pregnancy and the start of chemotherapy therefore appears to influence the prognosis independently of hCG values, the prognosis becoming worse as the interval increases.

6.4.9 *Type of antecedent pregnancy*

It is recognized that GTD occurring after term pregnancies virtually always prove to be choriocarcinoma, that those following non-molar abortions usually prove to be choriocarcinoma, whereas those following HM include many IM. Given that the prognosis for choriocarcinoma is much worse than for IM, a case exists for scoring non-molar antecedent pregnancy or morphologically confirmed choriocarcinoma as an adverse factor for both of these conditions.

6.4.10 *Site of metastases*

There is general agreement that metastases in the brain and liver are adverse factors. Gastrointestinal tract metastases are an adverse factor particularly because of the risk of severe haemorrhage in the early stages of treatment. Renal or splenic metastases may also prove difficult to eradicate.

6.4.11 *Size of tumours*

As with other cancers, large tumours prove more difficult to eradicate than smaller ones (*109*). Tumours of less than 3 cm diame-

ter have no additional effect on prognosis; those of 3–5 cms have a modest adverse effect; those greater than 5 cm have a greater adverse effect. The size of tumour metastases is part of the total tumour burden and is therefore reflected in hCG values.

6.4.12 *Number of metastases*

As previously discussed, a few small pulmonary metastases or a vaginal nodule may be seen in patients with HM and these may regress spontaneously. Massive molar embolization also needs to be distinguished from true metastatic disease. On the other hand, large numbers of small metastases may reflect an episode of wide dissemination and may be followed by rapidly progressive disease. The number of metastases may also be a component of the tumour burden and correlate partially with hCG values.

6.4.13 *Prior therapy*

The treatment of patients who have received inadequate therapy previously has long been recognized to present difficulties and to be associated with a high frequency of drug-resistance. This may reflect both the selection of difficult cases and inappropriate treatment protocols. It is apparent that "prior therapy" may refer to anything from the use of a single agent to the use of all known agents. A variable prognostic factor is therefore likely to be required to take prior therapy into account.

6.4.14 *Lymphocytic infiltration of tumour*

A marked mononuclear cell infiltration in choriocarcinomas has been associated with a more favourable outcome than with tumours showing little mononuclear cell infiltration (*104, 141, 142*).

The proportion of patients for whom the tumour is available for morphological examination is now quite low, so that it is only possible to score for this factor in a minority of cases.

6.4.15 *Patient's immunological status*

Patients with advanced disease were often found to be immunosuppressed (*143, 144*), and this may be a serious adverse factor. However, assessment of immunological status requires several days of observation, resulting in a delay before treatment is started that cannot be justified. Newer *in vitro* methods may be useful.

6.5 Summation of prognostic factors: scoring system

Having defined a set of prognostic factors for a heterogenous group of patients, it becomes necessary to devise a way to make use of such complex information. So far, the commonest way of using prognostic factors has been simply to put a patient in the poor-prognosis group because of a single unfavourable risk factor. However, this does not resolve the question of whether several slight adverse factors add up to equal one serious adverse factor. It also leaves unresolved just how bad a patient's prognosis may be.

The major problems in using prognostic factors are the weight to be applied to each factor and the way in which the effects of the different factors interact. One form of scoring system (Table 7) (*109*) has proved useful in several centres and in the light of further experience, can be simplified. A weighting is applied for each factor and each is assumed to act as an independent variable and their effects are assumed to be additive. The possibility of interactions needs to be further explored.

Table 7. Scoring system based on prognostic factors

Prognostic factors	Score[b]			
	0	1	2	4
Age (years)	≤39	>39		
Antecedent pregnancy	HM	abortion	term	
Interval[a]	4	4–6	7–12	12
hCG (IU/litre)	10^3	10^3–10^4	10^4–10^5	10^5
ABO groups (female × male)		O × A	B	
		A × O	AB	
Largest tumour, including uterine tumour		3–5 cm	5 cm	
Site of metastases		spleen	GI tract	brain
		kidney	liver	
No. of metastases identified		1–4	4–8	8
Prior chemotherapy			single drug	2 or more drugs

[a] Interval: time (months) between end of antecedent pregnancy and start of chemotherapy.
[b] The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score
≤4: low-risk
5–7: middle-risk
≥8: high-risk.

6.6 Clinical staging

Clinical staging of patients with GTT based on anatomical considerations, similar to that for other gynaecological tumours, has been proposed by Sung (*145–147*), and is under active consideration

by the International Federation of Gynecology and Obstetrics. The main goal is to achieve uniformity in the reporting of data from centre to centre, thus making results of treatment more comparable. Clinical staging does not attempt to assess the likelihood of a patient developing drug-resistance (the main goal of the prognostic scoring system), but similarity in outcome and prognosis between these two systems has been observed (*148*).

Clinical staging is based primarily on clinical examination and chest X-ray findings, thereby making it practical even in developing countries, where more extensive testing facilities may be lacking.

The clinical staging system that has been proposed is summarized as follows:

Stage I — the lesion is confined to the uterus without any metastases
Stage II — the lesion extends outside of the uterus, but is still confined to the genital organs
Stage III — the lesion has metastasized to the lungs
Stage IV — all other metastatic sites.

While the Group appreciated the desirability of encouraging uniformity of data reporting, it had reservations about a system that does not take into account the possible influences of antecedent pregnancy and tumour morphology, and that does not specify the methods for identifying extrauterine disease.

6.7 Recommendations for research

(1) Since identification of high-risk patients with GTT is important in determining appropriate therapy, further research in this area is needed. Risk-scoring systems, based on discriminant function analysis or similar techniques, should be developed using existing data and subsequently tested both retrospectively and prospectively.

(2) In view of the potential value of utilizing a staging system in standardizing the reporting of data, the Group recommends clinical testing of a staging system that is based on anatomical considerations. Because of differences in the prognosis of IM and choriocarcinoma, such a staging system should take into account the effects of tumour morphology and antecedent pregnancy.

7. PRIMARY MANAGEMENT AND FOLLOW-UP

7.1 Therapeutic modalities available

The principal therapeutic modalities are chemotherapy and surgery. The role of radiotherapy, if any, remains undefined. There is no evidence that the lesions are markedly radioresistant but retrospectively it has been the general experience that radiotherapy has contributed little to the management of many patients. There is no defined role at present for immunotherapy.

7.1.1 *Surgery*

Surgery has to be considered in the early stages of management in connection with:

— primary lesions in the pelvis,
— control of bleeding from vaginal/vulval metastases,
— brain metastases;

and in foci of resistant disease after chemotherapy, in connection with:

— uterus and adnexae,
— pulmonary and brain metastases,
— possibly metastases at other sites.

7.1.2 *Chemotherapy*

The most effective single agents are: methotrexate, dactinomycin (actinomycin D), and etoposide. Other useful agents include: cisplatin, alkylating agents—cyclophosphamide appears to have fewest disadvantages—vincristine,[a] 6-mercaptopurine, hydroxyurea, doxorubicin, bleomycin, and fluorouracil (used in China as a first agent).

7.2 Early surgical management

7.2.1 *Vaginal metastases*

The nature of these is usually self-evident and biopsy for histological purposes is rarely justified. Attempts to do so may be compli-

[a] Vinblastine and vindesine may be effective, but very few data are available and these drugs are more myelotoxic than vincristine.

cated by severe haemorrhage since numerous arteriographic studies have shown a connection between vaginal metastases and gross vascular changes in the pelvis (*149–151*). Bleeding vaginal metastases can usually be controlled by carefully placed purse-string sutures.

7.2.2 *Uterine or tubal perforation by choriocarcinoma or invasive mole*

Uterine or tubal perforation necessitates laparotomy and in many instances hysterectomy or salpingectomy. With IM affecting only a part of the uterine wall, local resection of the uterine wall and repair is possible (*152, 153*). Routine oophorectomy is not indicated and large theca-lutein cysts may be decompressed.

7.2.3 *Elective hysterectomy*

This is discussed elsewhere in relation to hydatidiform mole (section 4.5.3).

Patients with clinical evidence of choriocarcinoma and a uterine mass are subjected to hysterectomy in some centres but not in others (*107, 154*). If distant metastases are demonstrable, hysterectomy as an initial elective procedure has disadvantages if the lesion is choriocarcinoma. It may lead to further dissemination of the disease, and it delays the introduction of chemotherapy by 10–14 days, during which time the metastases progress and brain metastases may be seeded. It may have some advantage as a "debulking" procedure but it is not without operative risk if the tumour is large and adherent. However, it was agreed that there are different opinions concerning hysterectomy and that more data are needed.

For patients without demonstrable metastases, elective initial hysterectomy may be a reasonable policy if there is no wish to retain reproductive capacity. However, it still carries a risk of dissemination and close follow-up is essential.

Patients with histologically confirmed placental site tumours may require early hysterectomy if it is demonstrated that the tumour is drug-resistant or if there is an associated nephrotic syndrome (*120*).

Initial surgery for brain metastases is discussed elsewhere (section 7.5). Initial surgery at other sites is usually inadvertent because the diagnosis was not considered or was in question. A positive test for hCG establishes the diagnosis of trophoblastic tumour provided that

pregnancy is excluded and that steps are taken to exclude a germ-cell tumour and ectopic hormone syndrome.

Uterine haemorrhage usually responds to chemotherapy in a few days, and is not in itself an indication for hysterectomy.

Gastrointestinal bleeding from metastatic disease may be due to multiple small lesions and is best treated by transfusion and chemotherapy. Attempted surgical resections may fail particularly if chemotherapy has to be used within 10–14 days because of disease at other sites.

It has been reported by some groups (*155*) that surgical intervention during chemotherapy was not complicated by impaired wound healing or increased postoperative complications. A contrary view and a recommendation to avoid chemotherapy for 10 days before and after major surgery has also been made (*52*). Modest "single-dose" therapy at the time of surgery may minimize the risk of dissemination after surgical handling without impairment of wound repair (see section 7.3).

7.3 Surgery for drug-resistant disease

Patients with extensive choriocarcinoma sometimes respond to chemotherapy with the disappearance of all disease, except at perhaps one or two foci revealed by hCG values persisting above the limits of detection. Residual foci may be demonstrated radiologically and are more likely to be identified by tomography and computerized tomography (CT) than by plain X-ray. However, radiological methods do not distinguish between a viable residual tumour and non-viable masses. Opacities may persist on chest X-rays for more than a year after the completion of chemotherapy, but so long as hCG is undetectable they can be conservatively managed. Radioimmunolocalization may also help to locate minimal residual disease after chemotherapy and may help to distinguish a viable from a non-viable tumour (*156*).

When residual foci of disease associated with persistently high levels of hCG do not appear to be responding to any form of chemotherapy, surgical excision is indicated (*52*). Residual active disease in the uterus and adnexae may be suspected on the basis of ultrasound and/or arteriographic examination. If hCG is detectable and the patient has not had a hysterectomy, but has no evidence of

disease foci elsewhere, then hysterectomy may be necessary even in the absence of a lesion demonstrable by ultrasound or arteriography. However, as chemotherapy has improved, late hysterectomy with or without additional pelvic resection has become less frequently successful in removing residual tumour.

Residual foci of active disease in previously large pulmonary metastases may still be found in a few patients, and surgical intervention may result in complete and sustained remission (*157–160*).

The incidence of disseminated disease following surgical procedures may be reduced without impairing wound healing by giving methotrexate, 50 mg intravenously (total dose), during the operative procedure; 12 mg of calcium folinate (folinic acid) should be given 24 hours later and repeated if there is any elevation of blood urea or if urinary output falls below 2 litres per 24 hours. Alternatively, 0.5 mg of dactinomycin may be given i.v. during the surgical procedure, taking care to avoid extravasation.

7.4 Chemotherapy

The main purpose of defining the prognosis in patients requiring chemotherapy for trophoblastic tumours is to match their treatment to the risk of drug-resistance. So far as therapeutic response is concerned there is a more or less continuous spectrum of trophoblastic tumours, ranging from those that can be eliminated by modest non-toxic therapy to those that are at, or beyond, the present capacity to eradicate and have a high potential to become resistant. Some groups have opted for a 2-way division of patients into low- and high-risk groups (*134, 138, 161*). Others have opted for a 3-way division of patients into low-, medium-, and high-risk groups (*162*). These classifications should be based on a proper assessment of prognostic factors and a scoring system. In addition, it is important at the outset to determine whether the patient has brain metastases (see discussion on brain metastases, section 7.5).

7.4.1 *Therapy of low-risk patients*

Most patients in this category are those receiving chemotherapy within 6 months of evacuation of a complete HM, but as discussed

elsewhere, the criteria for treatment—and therefore the proportion of IM to choriocarcinoma—vary greatly between series.

There now seems to be general agreement on the value of a regimen using moderate-dose systemic methotrexate and calcium folinate (folinic acid) (a combination often known as MX/FA) in this group of patients, provided that renal and hepatic function are normal (*52, 163–166*). These regimens have been in use since 1962 and have sometimes been given by the intra-arterial route (*163, 167, 168*). The regimen may be based on a standard dosage, body weight, or calculated surface area. Calcium folinate increases the safety margin in these regimens and for most patients its use diminishes mucositis. There are, however, some exceptions so that increased calcium folinate or reduced methotrexate dosage may be required in subsequent courses. Variable absorption of oral methotrexate makes this route of administration inadvisable. In addition, oral methotrexate may be associated with increased toxicity. Methotrexate with calcium folinate (MX/FA) may be slightly less effective than methotrexate alone, but it was the view of the Group that the greater safety margin resulting when calcium folinate is given more than compensates for this.

In general, patients treated with MX/FA alone suffer no alopecia, have little mucositis or other toxicity, and minimal leukopenia. Pleuritic chest pain from methotrexate pleurisy sometimes occurs and mild blepharitis is common. Marked elevation of liver enzymes occurs in some patients in response to methotrexate. It is then usually advisable to change to dactinomycin or to a middle-risk regimen, excluding the methotrexate/mercaptopurine regimen.

A regimen consisting of a single intravenous injection of dactinomycin daily for 5 days is an alternative to MX/FA for low-risk patients. Extravasation of dactinomycin causes painful local lesions. Dactinomycin is tolerated well by some patients but may cause mucositis, nausea, vomiting, diarrhoea, myelosuppression, and alopecia in others. Pigmentation of the skin occurs with repeated courses, but is usually reversed on the completion of therapy.

It should be noted that hCG values in serum or urine may increase during the first 10 days or so after starting treatment. Thereafter, hCG values should show at least a 10-fold fall (i.e., one logarithmic fall) every 2 weeks. The interval between treatments should be kept as short as possible consistent with safety; in general, MX/FA and dactinomycin courses can be given starting on days 1, 14, 28, etc. For low-risk patients who respond to these regimens

satisfactorily, courses should be continued at the same intervals until hCG has been undetectable for 6 weeks. Menstruation usually resumes before or soon after therapy has been completed.

Patients treated with a low-risk regimen and whose hCG values do not fall to the limit of detection, or where there are rising hCG values while on treatment, are transferred to other protocols. For some patients, dactinomycin may be the only other drug required if there are no other adverse factors. If, however, resistance to MX/FA is seen early or if there are other adverse factors, the patient should be transferred to a medium- or high-risk regimen. A low-risk patient should not be changed from MX/FA to dactinomycin, or vice versa without a specific reason.

Examples of typical chemotherapeutic regimens are given at the end of this section and the abbreviations used below refer to these listed regimens. In all cases follow-up remains essential.

7.4.2 *Therapy of medium-risk patients*

The MAC III protocol that has been used in Boston, USA, for patients in both the medium- and high-risk categories, combines the two low-risk protocols with cyclophosphamide.

With the EHMMAC protocol the principle is to introduce a range of drugs sequentially. They are used in relatively simple combinations so as to keep toxicity to a moderate level (*164*). This protocol introduces etoposide, hydroxyurea + methotrexate + mercaptopurine, dactinomycin, vincristine + cyclophosphamide in sequence over a period of several weeks and the sequence is then repeated.

With both these protocols toxicity is greater than with the low-risk regimen. Etoposide is a potent agent for trophoblastic tumours (*169*). Cyclophosphamide and etoposide both produce alopecia, which is likely to be complete. Moderate leukopenia and thrombocytopenia may occur; nausea and vomiting are variable. A high fluid intake should be maintained in patients receiving methotrexate or cyclophosphamide.

The sequence of courses in EHMMAC is probably not critical, but the same sequence should be maintained for the individual patient. The interval between courses is generally 7 days, but occasionally needs to be longer. If administration of one of the drugs causes undue subjective toxicity or hepatic toxicity, or if it is ineffective in reducing hCG values, it may be omitted.

If hCG values fall only slowly or fail to reach the limit of detection the patient should be transferred to a high-risk regimen.

Patients in the middle-risk category should continue therapy for 8–10 weeks after hCG has become undetectable.

7.4.3 *Therapy of high-risk patients*

Much experience has been gained in various parts of the world with the CHAMOCA regimen, which brings together most of the agents known to be effective against choriocarcinoma. It uses a moderately high dose of methotrexate in order to get penetration of the drug into the central nervous system. It is a toxic regimen causing mucositis, alopecia, leukopenia and thrombocytopenia, nausea, and vomiting in most patients (*164*). The interval between courses should be kept as short as is consistent with safety and is generally 9–14 days. An earlier protocol (CHAMOMA) used melphalan but prolonged myelosuppression led to the substitution of cyclophosphamide for melphalan. Other modifications have been introduced (*161, 170*). It is often necessary to omit the final day (day 9) of the course because of toxicity.

The intervals between treatment should not be extended except for serious toxicity. CHAMOCA may be alternated with a less toxic regimen to minimize cumulative toxicity. Etoposide (EHMMAC, regimen 1, middle-risk) is suitable for this purpose. Although the CHAMOCA regimen has been given on an outpatient basis, it usually requires hospitalization.

To reduce the need for hospitalization and to see whether, taking advantage of the drug etoposide, a less toxic regimen could be as effective as CHAMOCA, an alternative schedule (EMA-Co, see page 65) has been introduced. Present indications are that it is at least as effective as CHAMOCA and is more acceptable to patients. Preliminary results with EMA-Co have been reported under a previous acronym (MECA) (*169*), and this regimen is now preferred to CHAMOCA where etoposide is available.

Patients not responding to other drugs may respond to cisplatin (*169, 171, 172*). In contrast to germ-cell tumours, the response of gestational choriocarcinoma to cisplatin after other drugs have been used is less predictable. If a satisfactory response is not seen within 14 days of cisplatin therapy it is probably not worth using it again.

The risk of resistance to cisplatin may be reduced by combining it with other drugs. Care is needed, however, and two nephrotoxic

drugs such as methotrexate and cisplatin should not be given at the same time. In addition to myelosuppression, cisplatin causes severe vomiting, dehydration, nephrotoxicity, and ototoxicity. Anti-nauseants may help. Cisplatin should only be given on an in-patient basis with full hydration and preferably with weigh-bed facilities. Magnesium supplements are likely to be required (*173*).

Treatment of patients in the high-risk category should continue for 12–14 weeks after hCG has become undetectable.

7.4.5 *Other agents*

A range of drugs isolated in China have been reported to be effective in patients with trophoblastic tumours (*174*). This group has also found mercaptopurine and fluorouracil to be valuable.

7.5 Central nervous system metastases

Brain metastases should be confirmed or excluded in all patients at the start of chemotherapy (*175*). Computerized tomography (CT) scanning is a major advance in their detection, but serum/spinal-fluid ratios for hCG are as sensitive (*176, 177*). Spinal fluid cannot, of course, be taken if there is evidence of raised intracranial pressure. *Patients found to have brain metastases at the outset require special care* (*178*). On the one hand, rapid necrosis of brain metastases may be complicated by intracerebral haemorrhage, while on the other, failure to get enough drug into the brain may lead to later drug-resistance. Methotrexate is the drug of critical importance (*52, 175, 178–180*). These patients are almost invariably in the high-risk category and it may be advisable to reduce the intensity of the initial drug regimen to reduce the risk of precipitating intracranial haemorrhage. The methotrexate dosage in the CHAMOCA and EMA-Co regimen is the minium required to reach an effective drug concentration in the nervous system.

With the second course of therapy it may be advisable to increase the dose of methotrexate to 1 g or 1 g/m^2, and to increase the calcium folinate to 30 mg, 12-hourly × 6; close observation of renal function is essential with high-dose methotrexate (*175*), and a high fluid intake and output *must* be maintained.

The precise location of brain metastases by CT scanning has greatly improved the possibility of their surgical removal. This may be advantageous at an early stage in treatment.

With therapeutic regimens that do not contain enough methotrexate to produce an effective concentration in the central nervous system, intrathecal methotrexate (12.5 mg) should be given at regular intervals between the courses of systemic methotrexate. Thus with the CHAMOCA regimen, intrathecal methotrexate (12.5 mg) may be given on day 9 with additional calcium folinate on day 10; it should be repeated during intervening courses of etoposide. With the EMA-Co regimen intrathecal methotrexate is given on day 8 and calcium folinate on day 9.

The response is monitored by following the cerebrospinal fluid hCG values and by computerized tomography scanning. Therapy directed at brain metastases should be continued for 6–8 weeks after hCG has become undetectable in the cerebrospinal fluid. Some workers have found radiotherapy useful in combination with chemotherapy (*180, 181*), others have observed responses that were not sustained and have found chemotherapy and surgery more successful (*175*).

7.5.1 *Prophylaxis against brain metastases*

One of the commonest causes of failure in the management of trophoblastic tumours is the development of brain metastases during the course of treatment (*164*). Patients with pulmonary metastases are at risk of developing brain metastases as long as there are viable tumour cells in the lungs. There is still some risk even in the absence of identifiable pulmonary metastases.

Brain metastases developing during the course of chemotherapy tend to be resistant to drugs. To prevent brain metastases it is necessary to get an effective concentration of methotrexate into the central nervous system, preferably at not less than 2-week intervals and to maintain this until the lung fields are clear or until serum hCG has become undetectable. The CHAMOCA and EMA-Co regimens provide adequate concentrations for this purpose. Intrathecal methotrexate (12.5 mg) should be given on day 9 of the CHAMOCA regimen and on day 8 of EMA-Co. Calcium folinate should be given (6 mg) 24 hours later. Since the use of prophylactic therapy, the incidence of late brain metastases has been significantly reduced (*175*).

7.6 Monitoring hCG level as an indicator of response to therapy

A sensitive (less than 5 IU hCG/litre) and highly reproducible assay system is essential and the level of cross-reactivity with luteinizing hormone should be known. Serum markers should be estimated twice weekly during treatment and results should be available ideally within 24 hours.

At the start of treatment it is not uncommon for hCG values to increase initially, and it may be 10–14 days before they start to fall. The hCG values cannot fall faster than the metabolic rate of clearance of the hormone, and the maximum halving time is 24–36 hours. Resistance to a therapeutic regimen is indicated when the hCG value 7–10 days after the end of the regimen is not significantly lower than the value at the start, but allowance must be made for assay variation, error, contamination, etc.

Treatment should be continued for 6–14 weeks after hCG values have become consistently undetectable. The shorter period applying to low-risk patients and the longer period to high-risk patients.

7.7 Recommendations

(1) The Group recommended that centres involved in the management of gestational trophoblastic tumours that do not have specialized chemotherapists should restrict the chemotherapeutic regimens used to those that have been shown to be effective and appropriate. Guidelines have been set out by the Group and examples of tested regimens are provided.

(2) The preliminary testing of new therapeutic agents and regimens is best carried out in trophoblastic tumour centres that have specialized chemotherapists and facilities for pharmacokinetic studies. When promising new agents have been identified it may be advantageous to establish multicentre trials in order to achieve effective evaluation in a wider setting.

7.8 Examples of chemotherapeutic regimens[a]

(1) *Regimens for low-risk patients*

(*a*) *MX/FA*

methotrexate,	50 mg (or 1 mg/kg with maximum of 70 mg) by i.m. injection repeated every 48 hours × 4

[a] The original acronyms have been retained in this report, although the names of the component drugs are given in the form of the International Nonproprietary Name.

Calcium folinate, 6 mg, 30 hours after *each* injection of methotrexate by i.m. injection or orally.

Courses repeated after a 1-week interval without treatment, i.e., days 1, 14, 28, etc.

(*b*) *Dactinomycin*

Dactinomycin, 0.5 mg (or 12 μg/kg) i.v. daily for 5 days.
Courses repeated after a 1-week interval without treatment, i.e., days 1, 14, 28, etc.

(2) *Regimens for medium-risk patients*

(*a*) *MAC III*

day 1	methotrexate	1 mg/kg i.v.
	dactinomycin	12 μg/kg i.v. (not to exceed 1 mg)
	cyclophosphamide	3 mg/kg i.v.
day 2	calcium folinate	0.1 mg/kg i.m. (24 hours after methotrexate)
	dactinomycin	12 μg/kg i.v.
	cyclophosphamide	3 mg/kg i.v.
day 3	As day 1	
day 4	As day 2	
day 5	As day 1	
day 6	calcium folinate	0.1 mg/kg i.m.
day 7	methotrexate	1 mg/kg i.m.
day 8	calcium folinate	0.1 mg/kg i.m.

Courses should be repeated at intervals of 14–17 days depending on recovery from toxicity.

(*b*) *EHMMAC*

Regimen 1 (etoposide VP 16–213)
100 mg/m^2 in 200 ml saline by i.v. infusion over 30 min daily for 5 consecutive days.

Regimen 2 (HC, MX/FA, MP)

Day 1 hydroxycarbamide, 0.5 g repeated after 12 hours (2 doses) orally

Days 2-8 methotrexate 50 mg i.m. or i.v (1 mg/kg max. 10 mg)
calcium folinate, 6 mg i.m. or orally 30 hours after each dose of methotrexate,
mercaptopurine, 75 mg daily on calcium folinate days only.

Regimen 3 (dactinomycin)
dactinomycin 0.5 mg (or 10–12 μg/kg) i.v. daily for 5 days.

Regimen 4 (VC, CY)
vincristine, 1 mg/m² on days 1 and 3
cyclophosphamide, 400 mg/m² i.v. on days 1 and 3.

The sequence of regimens in EHMMAC is 1, 2, 3, 4, 1, 2, etc.

Alternatively, regimen 4 may be held in reserve, to be used if one of the other regimens proves ineffective or toxic. The preferred sequence then is 1, 2, 3, 2, 1, 2, 3, etc.

The interval between the end of one course and the start of the next should not be less than 7 days or more than 10 days, but some extension is sometimes necessary.

(3) *Regimens for high-risk patients*

(*a*) *CHAMOCA*

day 1		hydroxycarbamide, 0.5 g, q.d.s., for 24 hours
day 2	10h00	vincristine, 1.0 mg/m²
	15h00	methotrexate, 100 mg/m², stat, i.v. methotrexate, 200 mg/m², 12-hour infusion
day 3	15h00	calcium folinate, 15 mg, i.m. or orally
day 4	08h00	calcium folinate, 15 mg, i.m. or orally
	10h00	cyclophosphamide, 600 mg/m² dactinomycin, 0.5 mg
	15h00	calcium folinate, 15 mg, i.m. or orally

day 5	08h00 10h00	calcium folinate, 15 mg, i.m. or orally dactinomycin, 0.5 mg
day 6	10h00	dactinomycin, 0.5 mg
day 7		No treatment
day 8		No treatment
day 9		doxorubicin, 30 mg/m^2, i.v.[a] cyclophosphamide, 400 mg/m^2

The interval between the end of one course and the start of the next is generally 10–15 days.

(*b*) *EMA-Co*

This regimen consists of two courses. Course 1 is given on days 1 and 2. Course 2 is given on day 8. Course 1 may require overnight admission, course 2 does not.

Course 1 (EMA)

day 1 etoposide, 100 mg/m^2 by i.v. infusion in 200 ml saline
dactinomycin, 0,5 mg, i.v. stat.
methotrexate, 100 mg/m^2, i.v. stat.
200 mg/m^2 by i.v. infusion, 12 hours

day 2 etoposide, 100 mg/m^2 by i.v. infusion in 200 ml saline over 30 min
dactinomycin, 0.5 mg, i.v. stat.
calcium folinate, 15 mg, i.m. or orally every 12 hours for 4 doses beginning 24 hours after starting methotrexate

Course 2

day 8 vincristine, 1.0 mg/m^2, i.v. stat.
cyclophosphamide, 600 mg/m^2, i.v. in saline

These courses can usually be given on days 1 and 2, 8, 15 and 16, 22, etc., and the intervals should not be extended without cause.

[a] Check that white blood cell count is greater than 2×10^9/litre and platelets greater than 80×10^9/litre before administering the drug. It may also be justifiable to proceed with lower counts in some circumstances.

(*c*) *(CV, MX/FA, cis-plat) ("OMP")*

day 1 vincristine, 1 mg/m², i.v. starting 5 hours later
methotrexate, 300 mg/m² is given by i.v. infusion in 500 ml normal saline during 12 hours

day 2 calcium folinate, 18 mg, i.m. or orally 24, 48 and 72 hours after start of methotrexate infusion

day 3 1 litre normal saline + 1 litre 5% dextrose overnight

day 4 cisplatin (NSC – 119875) 120 mg/m², i.v. with mannitol 12.5 g, i.v., then mannitol 10 g hourly × 6, with hourly infusions of 1 litre of normal saline (+1 g KCl), alternating with 5% dextrose (+1 g KCl) and a total of 3 g of magnesium sulfate.
Fluid and weight monitored.

An interval of 10–14 days is generally required before further treatment can be given.

8. FOLLOW-UP, CONTRACEPTION, FUTURE FERTILITY, AND LATE SEQUELAE

8.1 Follow-up

Follow-up schedules may be adjusted according to the estimated risk of relapse, but a standardized follow-up schedule is desirable, as follows:

Serum/urine for hCG—every 2 weeks up to 6 months after treatment, monthly up to 2 years after treatment, 3 monthly up to 4 years after treatment, and then 6 monthly.

Where close follow-up by hCG measurements is possible a single clinical examination about 6 weeks after completing therapy is all that is necessary. Communication between the treatment centre and the patient is, however, highly desirable for reassurance and support.

If at the time of completing treatment there is still radiological evidence of residual tumour, further radiographs are required. It may take 2 years for evidence of residual metastases to resolve.

Following hydatidiform mole the duration of follow-up varies. A wait of 2 years is often recommended after mole before another pregnancy, but with good assays and regular monitoring of hCG a further pregnancy may be allowed when the hCG values have been known to be normal for 6 months. The estimated risk of choriocarcinoma complicating a subsequent pregnancy is about 1:500.

Most centres agree that it is better to wait for a year after chemotherapy before another pregnancy is started.

8.2 Contraception

The question of fertility regulation for women who have been advised to avoid pregnancy for a period following HM or treatment for IM and CC has not been adequately dealt with in any study. Studies are necessary that will answer the questions posed in the following discussion of currently available fertility-regulating methods.

8.2.1 *Combination oral contraception*

In a report from the United Kingdom (*76*), evidence has been presented suggesting that women with HM who used oral contraception before hCG levels had regressed were more likely to need subsequent chemotherapy than women who did not use this method. A contradictory report (*182*) suggests that oral contraception may be used safely during the period of hCG regression after HM. As neither report contains any data on the varieties of oral contraceptive used by the women and, in particular, no information on estrogen dosage, the issue remains unresolved.

At one centre, oral contraception was thought to be responsible for increasing the risk of drug-resistance during therapy and for increasing the risk of subsequent relapse (*76, 107*); this method is therefore not recommended during 6 months after the end of treatment.

For many women, oral contraception may offer the advantages of convenience, effectiveness, and minimum side-effects, particularly when the duration of use is limited and the method is intended only to delay a return to fertility. However, until the issues raised above are resolved it is difficult to advocate the use of combined oral

contraceptives before hCG has become undetectable. Once this has happened there is nothing to suggest that oral contraception has any effect on prognosis.

8.2.2 *Progestogen-only pills*

There are no published data concerning the use of this method following HM, IM, or CC. Although less effective than combined preparations, this method has many of the same advantages. If the estrogen component of combined oral contraceptives is thought to carry an added risk during the period of hCG regression, there may be a case for the use of an oral progestogen-only preparation until hCG has become undetectable, with combined oral contraception being introduced afterwards.

8.2.3 *Long-acting progestogens*

Again no information has been published concerning the use of depot-medroxyprogesterone acetate or norethisterone enantate in women following CHM, IM, or CC. These preparations are in widespread use in a number of national family planning programmes, including countries where CHM is thought to be common, and it would be expected that a number of women might choose this method. Difficulties with long-acting progestogens might arise in patients with bleeding disturbances. The clinical significance of the bleeding would be resolved by hCG assay, but the long period of action of these preparations cannot be avoided. Lack of data prohibits any firm recommendation concerning the use of these compounds.

8.2.4 *Intrauterine devices (IUDs)*

Objections to IUD use have included the risk of uterine perforation, diagnostic confusion if irregular uterine bleeding occurs, and an unspecified potential risk posed by a foreign body in the uterus (*182*).

Uterine perforation should only occur rarely when insertion is carried out by experienced individuals, and should be no more frequent following CHM than following any other pregnancy. The confusion that might arise if irregular uterine bleeding occurs could be resolved by hCG assays. The potential risk of a foreign body

inserted into a uterus which possibly contains a tumour cannot be assessed on the available data and, as the authors who have raised this question do not describe the nature of the risk, speculation is pointless.

For some women for whom oral contraceptives are unsuitable and who wish to retain at least the prospect of future fertility, as well as for younger women who might choose the method, the use of an IUD seems reasonable.

8.2.5 *Other methods*

Barrier methods—condom or diaphragm—with or without the use of spermicides clearly present little, if any, risk. However, these methods are less effective then hormonal contraceptives or IUDs and, in some communities, their acceptability may be low.

Natural family planning may be an acceptable method for couples who are well motivated to its use despite its lower effectiveness. If there is a significant period of anovulation, the basal body temperature method would be inappropriate and the sympto-thermal method should be used.

8.2.6 *Surgical contraception*

For couples who do not wish a further pregnancy, a permanent method of fertility regulation is appropriate. Whether this takes the form of sterilization—by minilaparotomy or laparoscopy, hysterectomy, or vasectomy—should be determined for each couple taking other prognostic factors into account.

8.3 Future fertility and pregnancy outcome

The possibility that cytotoxic drugs may cause infertility and/or increase the occurrence of congenital abnormalities is an important consideration when women of reproductive age are being treated.

Infertility has been reported after chemotherapy particularly for Hodgkin's disease (*183, 184*). However, pregnancies following treatment for trophoblastic tumours have been reported regularly since the early 1960s (*121, 185–188*).

The obstetric histories of 445 women successfully treated by chemotherapy for trophoblastic tumours between 1958 and 1978 have been studied (*188*). They had been followed for a mean of 7.4

years and their ages ranged from 14 to 55 years. All but 2 patients received methotrexate. The maximum doses of drugs following which pregnancies occurred were: dactinomycin 29 mg, vincristine 22 mg, cyclophosphamide 8 g, mercaptopurine 15 g, 6-azauridine 300 g, hydroxycarbamide 16 g, doxorubicin 200 mg, melphalan 27 mg, vinblastine 60 mg, methotrexate 4 g. Altogether 131 patients received combinations of four or more drugs. All but 7 of 214 women who tried to become pregnant succeeded and 85.5% of pregnancies resulted in a live-birth. There were 32 terminations; none was reported to be for suspected fetal abnormality.

There were 9 cases of congenital abnormality, recognized within 7 days of birth. The incidence of congenital malformations recognized within 7 days of birth in England and Wales, in the median year of the study 1974, was 1.97% and the incidence of stillbirths was 1.1%. The respective incidences in the study group were 2.85% and 2.5%.

Only 2 of 33 patients who had relapsed and been successfully retreated and only 14 of 69 patients whose treatment had lasted more than 6 months attempted subsequent pregnancies. Of the 131 patients whose combination therapy included an alkylating agent (cyclophosphamide), 46 became pregnant, but the dosage was lower than in studies reporting infertility.

An important factor may be the intermittent drug regimen used in the management of trophoblastic tumours since the 1950s. The overall fetal wastage of 26% compared well with the rates found in normal populations (*189*).

Children born after treatment for trophoblastic tumours are now approaching fecundity and it is important that the second generation offspring should be identified and examined for possible genetic damage.

The use of cytotoxic agents that are known mutagens in fertile women has not so far been demonstrated to have adverse effects on the offspring, but it is important that there should be an awareness of the dangers and that cytotoxic agents should not be used unnecessarily.

8.4 Malignancy following chemotherapy

The incidence of second malignancy has also been investigated in 458 patients treated for choriocarcinoma or invasive mole between 1958 and 1978 and having long-term follow-up (*190*). After a mean

period of 7.8 years since the start of treatment and a total of 3522 years at risk, 2 women had developed second neoplasms: one an acute leukaemia and the other a carcinoma of the breast. The expected number of cancers on the basis of rates for the United Kingdom was 3.5. It was concluded that there was no evidence of carcinogenicity from the schedules used in the term of observation, although the single patient with acute leukaemia had received intensive chemotherapy over a period of 13 months and this may have induced leukaemia.

8.5 Recommendations for research

(1) In view of the continued uncertainty concerning the effects of oral contraception on the development of sequelae following complete hydatidiform mole the Group recommended that a prospective study of a combination oral contraceptive containing 50 μg of estrogen should be initiated and that this treatment should be compared with a non-hormonal method.

(2) A similar study to determine the effects of depot-medroxyprogesterone acetate and/or norethisterone enantate should also be undertaken.

(3) These studies should be undertaken in centres where there are adequate numbers of patients with complete hydatidiform mole and the means to provide close clinical follow-up with regular, frequent hCG assays.

9. GENERAL RECOMMENDATIONS

The Scientific Group has made specific recommendations at the end of each section of the report where these are relevant to the topics covered. In addition the Group made the following general recommendations:

(1) *Definition of terms*: uniform terminology should be used by health care workers in the description of gestational trophoblastic disease. The recommended terminology has been adopted in this report.

(2) *Collection of data*: there is a general requirement for the systematic collection of data relevant to gestational trophoblastic disease in most parts of the world.

(3) *Treatment centres*: the nature of the trophoblastic diseases, their incidence and their treatments are such that there is a need for patients to be managed by, or in conjunction with, specialized teams in centres where the necessary experience can be acquired.

(4) *Availability of drugs*: every effort should be made to ensure that there is ready access in all settings to the chemotherapeutic drugs that may be needed to treat gestational trophoblastic diseases.

(5) *hCG assay*: efforts should be encouraged for the development of a sensitive, non-isotopic assay for hCG, particularly one that would meet the needs of developing countries. Until such an assay is developed, an attempt should be made to standardize assay procedures and reagents for radioimmunoassay of hCG.

(6) *Distinction between complete and partial hydatidiform mole*: a concise and simple guide to the morphological distinction between complete and partial hydatidiform mole should be produced and distributed widely, particularly to pathologists.

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