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A Study of its Pathology

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Preface

As its subtitle shows, this monograph is concerned in particular with the pathology of choriocarcinoma and the related neoplastic or possibly neoplastic disorders of trophoblast. The endocrinology, clinical investigation and especially treatment are features of the disease fully and well described in various places by many others much better placed and qualified than I to do so; it is my hope, however, that in the pages that follow the reader will find at any rate some direction to most of the leading work in these areas.

It is a pleasure to thank those many people who, directly or indirectly, have helped to make this book possible. Much of it has been written against the background of experience gained from my association with the Registry for Diseases of Trophoblast of the Royal College of Obstetricians and Gynæcologists, and to this body and its co-founders in establishing the Registry, the Pathological Society of Great Britain and Ireland, and the Association of Clinical Pathologists, and their respective Fellows and Members who have contributed material to the Registry, I am greatly indebted and correspondingly grateful. In this connection I would pay particular tribute to the late Mr. Alan Brews who, as the spokesman of the College most immediately concerned when the Registry was formed, infused the project with his characteristic enthusiasm; this has been maintained by the Scientific Committee of the College and not least by Dr. Magnus Haines whose support in the running of the Registry has been invaluable.

I am indebted also to many colleagues in many other countries, and in particular to those who, like me, were able under the ægis of the International Union against Cancer to take part in the highly successful Conference on Choriocarcinoma in Baguio, P.I., in 1965. This was the starting-point of a world-wide co-operation in thought and action amongst many workers that has been and seems likely to continue to be of immense value; their names appear in the U.I.C.C. monograph frequently mentioned in the text, and all have my grateful thanks.

I would mention also with gratitude the late Dr. W. F. Harvey and my former associate, Dr. James Lees, who together induced my interest in choriocarcinoma some 23 years ago, and, in more recent times, Dr. K. D. Bagshawe and Dr. W. B. Ober who, professionally and socially, have been and continue to be the most helpful and stimulating of colleagues. I am likewise grateful to my immediate colleagues, Professor A. C. Lendrum and Dr. W. Guthrie, for much of the time spent on this project has been gained at their expense in terms of teaching and hospital duties. The photomicrographs were produced by Mr. J. W. Corkhill, F.I.M.L.T., and the script prepared by Mrs. E. S. Cargill, and to both of these I pay warm tribute for their painstaking work. In the face of no

little delay on my part, the patience of Messrs. Heinemann Medical Books Ltd. and their Chairman, Dr. Raymond Greene, has been something to marvel at, and I do most gratefully acknowledge their understanding.

Finally, the debt of thanks I shall find hardest to repay is that to my wife and family. Their tolerance of all that the writing of this volume has entailed has been far greater than I had any right to expect; they above all have my gratitude.

W.W.P.

Introduction

Gestational choriocarcinoma, as a neoplasm, is histogenetically unique. It remains, in 1971, unique in another way; it is the first and still the only malignant neoplasm generally acceptable as curable after systemic spread has occurred. These facts may be interdependent, the response to chemotherapy being in some way just a function of the unique composition of trophoblast: if so, gestational choriocarcinoma and its cure by chemotherapy are not the precedent or prototype for cancer control that they appear to be or that we might hope. However, there are encouraging hints, as in the partial response of some other neoplasms to chemotherapy, that study of the metabolic processes involved in the undoubtedly successful chemotherapy of choriocarcinoma may indeed yield information relevant to cancer chemotherapy as a whole.

The histological diagnosis of choriocarcinoma has long been notorious for its imprecision, not because aberrant trophoblast is difficult to recognise but because the correlation between histological aberrancy and biological behaviour of neoplastic tissue on which the histologist bases his diagnosis (which is prognosis), is here extremely low; hence the old tenet "If the patient died (with multiple metastasis), she had choriocarcinoma; if she survived, she did not". This extremist position can no longer be sustained. Patients nowadays undoubtedly are cured of choriocarcinoma even if sometimes, as explained later, the evidence on which the diagnosis is based lacks the certainty that the scientist would like.

The ætiology of choriocarcinoma is obscure; so is that of most other malignant neoplasms but in few others is there so tantalising a situation as that presented by the remarkable geographical incidence of choriocarcinoma, strikingly frequent in many if not most tropical countries, notably rare elsewhere (with the curious exceptions of Japan, Korea and Taiwan). Its relationship with hydatidiform mole has long been recognised, and it is a strange relationship. There is certainly something analogous between the sequences "mole → choriocarcinoma" and "papilloma → carcinoma" but the analogy is far from complete and in consequence, if uncritically pursued, liable to mislead. Any investigation of the relationship can scarcely dodge the problem of the ætiology and histogenesis of hydatidiform mole itself. This remains unsettled. Much new information has emerged from recent cytogenetic and electron microscopic studies including, interestingly enough, a report of structures within molar trophoblast that have served to revive or resurrect the hypothesis of a viral ætiology.

The recent growth of interest in the immunology of transplantation has naturally brought with it increased interest in the status of the fœtus as an allograft and in the part played in this allograft relationship

by trophoblast whether physiological or pathological. Interplay of maternal and fœtal tissue-immunity factors there must be; what its significance is, and what the agencies are that normally sustain the symbiosis, are even yet being only faintly discerned, and no doubt there are many others still unknown. If, then, there exists some kind of controlling mechanism, we may fairly regard choriocarcinoma as one of its derangements, and therapeutic endeavour along immunological lines would be entirely rational. This has indeed been tried but with very uncertain result. In fact, the future of immunotherapeutic research as a whole, rational and logical though it be, is uncertain; it has been made so by the very success of chemotherapy. One further feature merits special mention in a publication intended as much for the general physician as the obstetrician/gynæcologist, namely, the outstandingly mimetic capacity of the neoplasm. Choriocarcinoma can produce signs and symptoms highly mimetic of other lesions and be not suspected, and because not suspected, be not detected, and because not detected, even though curable, be lethal. To be sure, such deaths are rare but there is scarcely one that could not be avoided.

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Chapter I

History

It is not surprising that a neoplasm as distinctive clinically and pathologically as gestational choriocarcinoma should have a history more dramatic than most; that its recognition and definition should have taken so relatively long, on the other hand, is surprising. The principal events are fairly well known—clinical recognition as a malignant neoplasm especially associated with pregnancy, uncertainty whether it was carcinoma or sarcoma, convincing demonstration of an origin in trophoblast, acceptance as chorionepithelioma in continental Europe, then Scotland and finally England—every stage attended by debate, often spirited and sometimes heated. Nevertheless a brief account of the affair is in order, not only for its intrinsic interest but also because many of the principles of reasoning and deduction involved are as applicable now in the definition of a pathological entity as they were then. A finely written and entertaining account of the "career" of choriocarcinoma was published not long ago by Ober and Fass (1961). I have leaned heavily on this article for much of what follows but warmly commend its reading in full.

Three cases of what was eventually shown to be choriocarcinoma were described in 1877 by Chiari; at that time the nature of the lesion was quite unknown. Chiari himself had regarded it as a carcinoma of the uterus of unusual type in young women recently pregnant. To the extent that the lesion was a carcinoma, Chiari was right but his choice of epithelium was wrong; the crucial association with pregnancy was thus missed. The sections of these cases were re-examined 13 years later by Pfeifer (1890) and correctly diagnosed as the malignant neoplasm peculiar to pregnancy that had been briefly described a short time before by Sänger (1889). However, as subsequent events showed, Sänger also was correct only in part. He had noted the resemblance of multinucleated masses, so frequent and prominent a feature of choriocarcinoma, to cells of decidua, and accordingly concluded that the lesion was a malignant neoplasm of that tissue, a "deciduoma malignum", a neoplasm of non-epithelial origin and thus a sarcoma: the fact that the neoplasm seemed so invariably to spread by the blood and not the lymph was regarded not unreasonably as good supporting evidence. Sänger's identification of the lesion as deciduoma malignum and his later published (1893) classification of the types of "deciduoma" were widely adopted, persisting for many years even in the face of steadily growing support for the interpretation and conclusions of another worker, the pathologist Felix Marchand, then in Marburg. In

Marchand's opinion the neoplasm was of trophoblastic origin. The matter was, of course, one of histogenesis and the possibility of a non-decidual chorionic origin had in fact been raised by an earlier worker. In 1893, Gottschalk stated his belief that cells of the chorionic villi were the essential neoplastic element but that they progressively induced an equally malignant neoplastic change in the cells of the decidua; that is, the neoplasm was a form of "mixed tumour". However, of the various cell elements, epithelial and stromal, that are present in chorionic villi, he identified those in the stroma as the source, and so concluded that the neoplasm was a "mixed sarcoma". In this he was wrong but at least he had raised the possibility that cells of chorionic type might be concerned.

In the following year, Marchand (1894), on the basis of his analysis of two cases, first presented his theory that the lesion was of trophoblastic origin and thus an "epithelioma". Both these cases, interestingly enough, were unusual; one was a choriocarcinoma of the uterine tube, eventually fatal; the other took the form of a fungating mass at the fundus of the uterus, the unusual features in this instance being not only its apparent cure by vaginal hysterectomy but also the fact that this was achieved despite incomplete excision of the mass (the patient, at any rate, was alive and well 12 months later; we must suppose that the remnant neoplastic tissue underwent spontaneous regression, the first authentic instance of this phenomenon). The uncommon location of the neoplasm in the first case, the uterine tube, may have been a significant if unwitting contributor to Marchand's analysis of the histogenesis to the extent that the amount of decidua developing around a conceptus in this site is usually remarkably small; the neoplastic tissue can then be seen unaccompanied, or, as it were, "uncontaminated" by decidua which otherwise, in the uterus, offers itself so strongly as a candidate for selection as the tissue of origin. This we do not know but, at any rate, Marchand then, and more fully later (Marchand, 1895), did describe the neoplasm as consisting essentially of the two types of tissue, multinucleated-syncytial and polyhedral-celled, that had long been known to characterise normal chorionic villi and had already been given the composite name of "trophoblast" by Hubrecht (1888). There remained, however, the still unsettled problem of the histogenesis of normal trophoblast, in particular whether both types of tissue, that is, both layers of epithelium covering the villi, were of fœtal origin. Marchand applied himself to this question for the next three years, including in his studies an examination of rabbit ova and their implantation sites as well as human material. He concluded that both layers were indeed fœtal in origin, and that what he had hitherto designated in his earlier writings as a "so-called decidual tumour" was in fact an epithelioma of trophoblast or, as he now termed it (Marchand, 1898), "chorionepithelioma".

With a few sporadic exceptions, Marchand's views were rapidly adopted in continental Europe, in centres in Scotland and, through the largely confirmatory work of Whitridge Williams (1895), in interested clinics in the U.S. English workers, however, remained unconvinced. Conflicting views were advanced and discussed, in particular at several meetings of the Obstetrical Society of London, where eventually a committee was appointed to examine and report upon the matter. This committee concluded in essence first, on grounds of morphology, that the neoplasm was a sarcoma, probably arising in maternal tissues and second, for no very clearly stated reason, that the tissue of origin was not decidua and that the lesion could not, therefore, be properly designated deciduoma malignum. These pronouncements prevailed very generally in England for the next seven years, but there were stirrings further north and these culminated in the presentation in 1903 by John H. Teacher of Glasgow to the Obstetrical Society of London of a dissertation on what he now firmly called chorionepithelioma (later published in extended version, Teacher, 1903). To quote the words of Ober and Fass (p. 69) "In the discussion which followed there was much heat. A distinct odor of phlogiston pervades the printed account." In this atmosphere, at times acrimonious, the discussion was adjourned to resume twelve days later, by which time virtually all were agreed that the original committee had been in error and that the Marchand–Teacher concept was correct. Unity was thus achieved, and no serious opposition to Marchand's deductions has been offered since then.

It is unfortunate that at the highly debatable stage when the original committee was set up by the Society, the matter was not considered by or handed over to morbid histologists for their views. None, least of all histologists themselves, would deny that morphological interpretation has its pitfalls, but most would concede that, even seventy years ago, problems of the histogenesis of neoplasms were more likely to be solved by pathologists than by clinicians. John Teacher's success as interpreter and peace-maker owed little, if anything, to freakish good fortune. He had been trained in Glasgow, then as now a school strong in pathological tradition, and had travelled widely in Germany in 1902 especially to acquaint himself with current thought on "deciduoma malignum". He had already, in 1898, along with his colleague Kelly (Kelly and Teacher, 1898) published an account of the lesion, and was even then strongly inclined to the view that it had its origin in chorionic tissue. By 1902 as already described, Marchand's histological interpretation of the neoplasm was well known and very generally accepted; with almost the sole exception of the gentlemen of the Obstetrical Society of London, chorionepithelioma was an established entity. As the Transactions show, Teacher's conversion of the Society to proper thinking was a model of courtesy, tact and generous understanding.

The way to the next great advance in the understanding of the lesion

followed the discovery by Aschheim and Zondek (1927) of the excretion during pregnancy of gonadotrophic substances in the urine. This led naturally to an investigation of the urine in patients with the lesions associated particularly with the placenta, hydatidiform mole and choriocarcinoma, and the excretion of gonadotrophin by such patients was reported almost certainly first by Zondek (1929); the prognostic value of its measurement, and particularly of its serial measurement, was first realised and emphasised by Rössler (1929). Serial urinary assays have, of course, remained one of the mainstays of clinical supervision and treatment of the patient with trophoblastic neoplasia ever since, even if an early hope, expressed by Rössler himself, that hormonal assay would distinguish between the harmless hydatidiform mole and the harmful hydatidiform mole has still, after 40 years, not been wholly fulfilled. Proof of the trophoblastic origin of the hormonal substance, and thus its designation as chorionic gonadotrophin, was obtained by tissue culture methods in the 1930's; its function as a "tumour-specific" marker or index substance has endowed hormonal research into trophoblastic neoplasia with a precision that for long was and still almost is unique.

A lesion as rare as choriocarcinoma cannot figure frequently in the clinical experience of one physician or even in the records of one hospital; or, rather, that was the situation until relatively recent times. The first formal plan to gather together cases of trophoblastic neoplasia, both hydatidiform mole and choriocarcinoma, led to the establishment in 1946 in the U.S. of the Albert Mathieu Memorial Chorionepithelioma Registry. By the generosity of Dr. Albert Holman of Portland, Oregon, this was founded in memory of his former colleague, Dr. Albert Mathieu, for many years Professor of Obstetrics and Gynecology at the University of Oregon Medical School and, right up to his death in 1939, an enthusiastic student and publisher of works on trophoblastic disease. The Registry, a comprehensive collection of histopathological material and clinical data, was located at first in the Department of Obstetrics and Gynecology at the Johns Hopkins Hospital under the supervision of the late Dr. Emil Novak, whose name will always be associated with the advancement of knowledge in this field. On Dr. Novak's death in 1957, the material of the Registry was removed to Chicago where it has since been in the Northwestern University Medical School under the care of Dr. John Brewer. The contributions made by this Registry over the years to the understanding of trophoblastic disease is great, and many of the papers quoted in the present volume were based on the abundant material within its files, as, for example, those by Novak and Seah (1954, 1954a), Schoen, Konwaler and Novak (1954), Park (1957, 1959), Brewer, Rinehart and Dunbar (1961), Brewer, Smith and Pratt (1963), Brewer *et al.* (1964) and Scott (1962).

A Registry along similar lines was formed in 1960 in the U.K. by

joint action on the part of the Pathological Society of Great Britain and Ireland, the Royal College of Obstetricians and Gynaecologists and the Association of Clinical Pathologists. It now consists of histopathological material and clinical data, including in most cases three years' follow-up information on some 700 patients. Analyses of the material in the Registry have already been published (Park, 1962, 1967).

Though hardly an "event", the unusually high incidence of hydatidiform mole and choriocarcinoma in certain tropical areas became recognised only during the early years after World War II, thanks mainly to a series of publications by Acosta-Sison in the Philippine Islands; as described later a similarly high incidence was soon reported elsewhere, for example, Indonesia, Japan and Taiwan. This stimulated the formation in the U.S. of a team of workers, largely under the ægis of the Armed Forces Institute of Pathology, who conducted the now well-known "Joint Project" of investigation into the matter. The outcome of this will be referred to presently, but it may be said meantime that the reason for this curious geographical variation is still undiscovered; the problem remains as tantalising as ever.

Choriocarcinoma is one of the most devastatingly malignant of all cancers. An historic event by any standard was the achievement of its cure, first described in detail by Li, Hertz and Spencer in 1956. At first, very properly, claims of cure were cautious: in fact, for many years the term was never used; patients who recovered and remained well without further treatment were held to be in "sustained remission". However, as years passed without recurrent trouble, and as occasionally treated patients achieved a successful pregnancy thereafter, the term "cure" did seem to be admissible; none now disputes its use. Choriocarcinoma thus became the first of the regularly metastasising lethal cancers to be rationally and predictably curable.

Chapter II

The Nature of the Neoplasm

Choriocarcinoma is the malignant neoplasm of trophoblast. This is a true statement but it is not a definition of the lesion. A strict definition of choriocarcinoma is in fact difficult to achieve. In part, the difficulty is owed to peculiarities intrinsic to the lesion; for the rest, the difficulty is that encountered in relation to any "cancer", the ancient problem of defining "malignant". There is really no satisfactory definition of "malignancy"; none can be framed that cannot be proved to breaking-point by some exception. However, it will suffice for present purposes if we regard as "malignant" a lesion consisting of tissue, histologically recognised as neoplastic, which, if untreated, will kill the patient by ever-widening metastatic spread; and it is, of course, in terms of some such definition that the histological diagnosis of choriocarcinoma, as of all other malignant neoplasms, has always been made. That is; a certain tissue pattern is identified and, from experience of the behaviour of such tissue in the past, recognised as one that betokens progressive, metastasising and ultimately fatal growth.

Despite fairly general agreement on this line of reasoning, it became clear from a very early stage that choriocarcinoma seemed to behave in a way quite unlike that of any other neoplasm. Figures for the incidence and curability of many malignant neoplasms have certainly always differed to some extent between one centre and another, even within the same country, but in none was there the range reported for choriocarcinoma. The differences, cure rates varying from some 80% to virtually nil, were far beyond any that could be reasonably explained in terms of differences in therapeutic procedure. It was thus natural that the validity of diagnosis should be called in question, and since, by analogy with other neoplasms, the diagnosis is or ideally should be based on the histopathology of the lesion, it was to the pathologist that others looked, and to some extent still are looking, for an explanation.

Part of the difference in figures for incidence and curability is undoubtedly owed to the use of different terminology, in particular the designation of the entity "invasive hydatidiform mole" (mola or chorioadenoma destruens) as a type of choriocarcinoma. At one stroke this abolishes the invasive mole, produces an apparently great increase in the incidence of choriocarcinoma and, since therapeutic results have always been relatively good in the treatment of the molar lesion, an apparently very much better cure rate for choriocarcinoma than in clinics where the invasive mole continues to be classified as a different

entity. This causes confusion and has little justification but is fortunately practised in only a few centres.

A further possible explanation for variability would be simply lack of familiarity with acceptably diagnostic criteria. Choriocarcinoma is rare and this lack would not be a surprising consequence: part of an early embedding normal conceptus, for example, has been diagnosed more than once as a choriocarcinoma (a not inexcusable error, incidentally, certainly not deserving of the ridicule it has sometimes received), and, *vice versa*, on one occasion at least ectopic trophoblast almost certainly part of a choriocarcinoma that caused death 2 months later was diagnosed as a previllous ovum (Freed and Chatfield, 1958). Simple misdiagnosis of this kind, mostly misinterpretation of abortion residues, probably still does occur sometimes but the total amount of it must be small. With the emergence of special centres and clinics for the treatment of patients with trophoblastic disease there is an increasing probability that any tissue on which diagnosis depends will be examined by one or more pathologists with at least a greater experience of trophoblastic histological aberrancy than the donor. How much nearer the truth than the donor their opinion may be is no doubt another matter; and indeed, any pathologist seeking further opinion from such a specialised centre, and having his own preferred view controverted, might fairly ask, What, then, *are* the truly diagnostic criteria of choriocarcinoma? This, of course, is the nub of the problem. Histological minutiæ will be analysed later; meantime it would be fair to say that still the problem is incompletely settled, still the search is maintained for reliably prognostic histological criteria. As just stated, histopathological diagnosis is based on a correlation between tissue patterns and type of clinical behaviour; the higher the correlation, the greater the degree of diagnostic accuracy, and with aberrant trophoblast the correlation remains disappointingly low. This is by far the most influential factor causing fluctuation and variability in the statistics of choriocarcinoma between different centres in the same country. There is no doubt that 2 patients may harbour within the uterus trophoblastic lesions of apparently identical histological aberrancy, have a virtually identical clinical history and be treated in an identical way, yet one will live and the other die with multiple metastasis. To be sure, this may happen with almost any malignant neoplasm but the accumulated experience of many workers over many decades has made unavoidable the conclusion that in this respect, as in so many others, choriocarcinoma stands alone: prediction of the outcome from the histology of neoplastic trophoblast as seen in uterine curettings or even the excised uterus (which should be seen less often nowadays) falls significantly short of the level of accuracy that can be achieved with almost all other malignant neoplasms. An illustrative example is contained in the article by Park and Lees (1950) where a report is given of 37 patients who, on histo-

pathological evidence, ". . . had been judged, certainly or tentatively, to have choriocarcinoma". Hysterectomy had been performed in 23 of these patients on the basis that ". . . the clinical findings had sufficiently conformed with the histologic diagnosis . . ." to warrant this procedure (this particular form of union between clinical and histological evidence is only doubtfully admissible and will be discussed later under "Diagnosis", p. 139). Of the remaining 14 patients, 9 did not have hysterectomy and were alive and well, in most instances several years later. Since these 9 patients had been regarded on histological grounds as "certainly or tentatively" having choriocarcinoma, they must stand as examples of over-diagnosis for it would surely be unreasonable to invoke on this scale the only other possible explanation, "spontaneous regression". The global extent of false-positive diagnosis of this kind is difficult to assess but, as explained above, with the increasing referral of patients having actual or suspected trophoblastic lesions to special centres the amount is almost certainly much less than it was some 20 years ago. However, it remains a fact that even amongst those with substantial histological experience of trophoblastic lesions, opinion still may differ as to whether or not an abnormal trophoblastic tissue pattern will or will not be followed by, or is likely perhaps already to be accompanied by, significantly invasive local growth and/or metastasis.

It seems appropriate therefore to analyse more closely the way in which the criteria customarily used to diagnose and define malignant neoplasia in general—*cytological aberrancy*, *invasiveness* and *metastasis* —are applicable in the case of abnormal trophoblast.

Assessment of *cytological aberrancy* is revealed at once as inadequate by the fact that with curetted material, where there is usually no myometrium by which to assess invasiveness, histological interpretation of the aberrant cytology is so variable. It might be hoped, then, that assessment of *invasiveness*, or of cytological aberrancy and invasiveness together, as is the practice in the diagnosis of most malignant neoplasms, would prove more helpful, but even here there are difficulties.

The fertilised ovum, as a blastocyst, obviously cannot embed itself within the endometrium without "invading" it. All trophoblast is therefore, in this sense, to some extent "invasive" and so, when these terms are used to describe the behaviour of trophoblast that is or may be neoplastic, they need to be qualified in some way, hence the phrase used above, "significantly invasive local growth". Excessive ingrowth into the uterine wall with deep, obviously unphysiological and perhaps total penetration of the myometrium is the distinguishing feature of the placenta accreta/percreta. This is beyond doubt "significantly invasive local growth" but in practice it rarely if ever causes confusion with trophoblastic neoplasia as we find it in association with the hydatidiform mole and choriocarcinoma; the chorionic villi of placenta percreta, even