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TROPHOBLAST AND ITS TUMORS

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Part I. Fundamental Concepts

HISTORICAL PERSPECTIVES ON TROPHOBLAST AND ITS TUMORS

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Two separate lines from the poem *Gerontion* by T. S. Eliot provide a fitting introduction to this monograph:

> "To lose beauty in terror, terror in inquisition . . . ."

and

> "History has many cunning passages, contrived corridors
> And issues . . . ."

I am tempted to apply the first of these passages to the subjective feelings of the microscopist as he examines trophoblastic tissue from a trophoblastic growth. The first impression is one of esthetic pleasure at the arrangement and disposition of cells, their tinctorial reactions, and their relations to the substance and stroma of the organ in which they are situated. The appreciation of histological beauty soon gives way to terror as the gravity of the situation for the patient becomes apparent. Neoplasms of trophoblast are notoriously dangerous and often unpredictable. They usually occur in young women, women of the childbearing age, and the clinical stakes are high. It is this feeling of terror as the microscopist examines a tumor of embryonal tissue which, I think, is one of the chief reasons why the malignant potentialities of trophoblastic proliferations are so often overestimated and the lesions overdiagnosed. The pathologist must always remember that trophoblast is an embryonal tissue, that even when not neoplastic it possesses the property of invading maternal tissue and blood vessels, and therefore will combine both the architectural and cytological appearances usually associated with malignant tumors. It follows that, to some extent, one must discount the malignant appearance of trophoblastic cells and cell aggregates in many circumstances. It is at this point that terror gives way to inquisition, that is, to the process of scientific enquiry, a process of observation and ratiocination designed to analyze the properties of the tissue, to relate the present instance to past experience, and to evaluate the possible behavior of the lesion.

In so doing it must be remembered that the properties to be studied are both functional and structural, that the morphologic aspects must be placed in the framework of the clinical aspects, and that the clinical framework must be supported by correlation with the morphologic evidence of biological events. Although as individuals we may elect to focus our attention on a specific property of trophoblast or upon a specific phenomenon in a given case or series of cases, the analytical process is somewhat artificial,

and synthesis or integration is necessary before the problem can be seen in all dimensions.

One of the most frequently neglected dimensions of the scientific process is time, the relation of the present instance to past experience. This becomes particularly apparent when one deals with a lesion infrequently encountered, an instance outside of daily experience. The rarity of trophoblastic tumors and the fact that few observers have had the opportunity to accumulate wide experience with them makes it necessary to evaluate individual instances in terms of other observers' experience. There are few items in the lexicon of oncology that require more consciousness of one's debt to one's scientific predecessors than does the problem of trophoblastic tumors. On reading earlier accounts, one becomes progressively aware that all the phenomena have been described before, even those that may strike the contemporary observer as original. The rich literature on trophoblastic growths includes many instances of the bizarre and exotic as well as those that are common to the process.

The value of historical perspective is the insight it furnishes for evaluating a case at hand or, alternatively, for planning and designing an experiment intended to isolate for study one aspect of the general problem. In the following exposition I shall select certain of the more important aspects of trophoblast and determine how many are contrived corridors. I shall try also to bring into focus some of the major unanswered questions, some of the cunning passages that require illumination before one can see where they lead.

The modern history of choriocarcinoma begins in 1895 with the work of Marchand,[1] who demonstrated that this malignancy was an epithelial tumor derived exclusively from trophoblast. Although the common name for choriocarcinoma at this time was deciduoma malignum, this should not be interpreted as indicating that all authorities then believed that choriocarcinoma was derived exclusively from decidua. Even Sänger,[2] whose views Marchand refuted, classified tumors associated with pregnancy as "(1) sarcoma decidua-cellulare, (2) sarcoma decidua-cellulare with participation of chorionic villi, and (3) malignant interstitial hydatidiform moles and placental polyps." Gottschalk[3] in 1894 dissented from Sänger's views and enunciated the doctrine that choriocarcinoma was a tumor of fetal tissue, a sarcoma of the chorion arising from the cytotrophoblast (Langhans' layer) and the stroma of the villi. Whereas Gottschalk labeled choriocarcinoma a sarcoma and considered cytotrophoblast as being of fetal mesoblastic origin, Marchand clearly stated that the tumor was derived from both syncytiotrophoblast and cytotrophoblast, both epithelial in nature. However, in his publication of 1895 Marchand adhered to the then prevalent idea that syncytiotrophoblast was of maternal origin and cytotrophoblast was of fetal origin (fetal epiblast), FIGURES 1 and 2. Subsequently, he modified this portion of his viewpoint and summarized it in 1903 in a remarkable but rarely quoted communication:[4]

"It is comprehensible that authors who first recognized tumours of this nature as something unusual, above all Sänger and Pfeiffer, should have

designated them as 'decidual sarcoma.' I may remark, historically, that to Gottschalk belongs the credit of having first rightly interpreted the masses of the so-called syncytium of the chorionic villi in a malignant tumour . . . but he erroneously regarded a part of the tumour as sarcoma arising from the stroma of the villi . . . By a specially fortunate circumstance it chanced

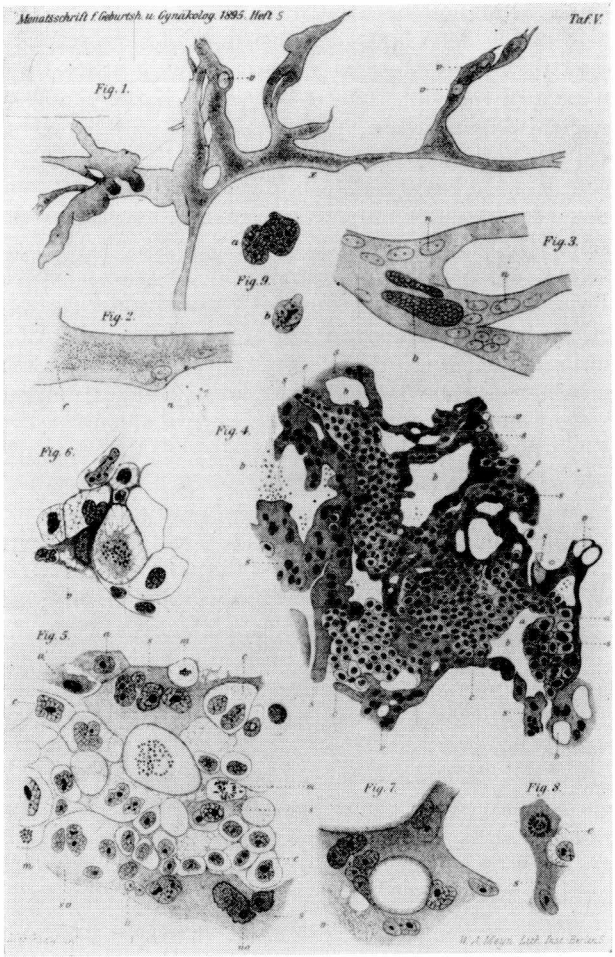

FIGURE 1. Reproduction of an illustration from Marchand's historical article.[1]

that I was able, in a case of hydatidiform mole of the uterus, to recognize the same epithelial formations as in the two layers of the chorionic mantle, and the invasion of the muscular wall of the uterus by these cells, as in malignant chorioepithelioma. A difficulty presented itself in forming an opinion upon the origin of the tissue forms present in this growth, viz., the very diverse opinions which existed upon the two layers of the chorionic epithelium . . .

While several embryologists held both layers to be fetal, others, having in view the conditions found in animals, referred the outer layer to a maternal, the inner layer to a fetal origin. Inasmuch as at that time I had not had the opportunity to decide this question by personal study of early human ova, I had to assent to one of these views, and I felt obliged to decide upon the latter, although I had already . . . pointed out that it was often impossible to make a distinction between cells arising from the superficial and those arising from the deep layer. I regard as of the greatest importance the observation that the malignant growth actually arises from the entire epithelial covering of the villi, that at least part of the new growth . . . is of fetal ectodermal origin, a view which was later to be strenuously opposed by a number of authorities."

It may be observed in passing that in Marchand's primary communication the conclusions were based on only 2 cases that he studied personally, one a choriocarcinoma following an ectopic tubal pregnancy, the other following a normal pregnancy. Marchand reviewed 26 previously reported cases of choriocarcinoma, 13 of which developed after hydatidiform moles, 7 after term pregnancies, and 6 after abortions. Marchand also described cases of a "atypical chorionepithelioma" that now are considered examples of syncytial endometritis. At this time he had not had the opportunity of studying examples of what now would be termed chorioadenoma destruens. This lacuna was filled by the observations of Apfelstadt and Aschoff[5] and Neumann[6] in 1896. In reviewing cases of this period, it is sometimes difficult to classify them according to our own contemporary criteria into the tidy compartments that our present nomenclature pretends to offer. Park and Lees[7] in their extensive review have implied that this difficulty exists. They state more explicitly the difficulties that Sänger, Gottschalk, Marchand, and Aschoff must have faced in deciding which elements were chorionic and which were decidual: "Trophoblast is quite distinctive, and so is decidua, yet if these two different and distinctive tissues are in contiguity, no sharp line can be drawn between them so that one can say that this cell or that cell is maternal or fetal."

I am sure that this difficulty has occurred to everyone who has examined placental sites with any care. The presence of Nitabuch's stria is helpful, but this boundary can be discontinuous and is of value only in intact specimens. Where there is any degree of penetration of the decidualized endometrium by proliferated trophoblast, the assignment of cells can be very treacherous indeed. Parenthetically, the presence of multinucleated cells is not helpful. While most of them are syncytiotrophoblastic, some are clearly decidual, and a few are derived from smooth muscle. Park and Lees[7] point out that vascular endothelium, cytotrophoblast, and endometrial glandular epithelium are also potential sources for "placental site giant cells," but in practice these are uncommon sources. The contemporary morphologist faces the same difficulty as did his predecessors at the turn of the century.

Marchand's ideas were accepted with only minor controversy. In 1898, Aschoff[8] published a fine critical *Referat* of the problem. Additional case

reports multiplied, and a further review by Münzer[9] in 1902 served to settle the issue insofar as the German school was concerned. In 1903 Teacher[10] reviewed the history of chorionic tumors, presented 3 additional cases of his own, and prepared an annotated list of 189 reported cases, all but 10 of which had been reported since 1888. Teacher's elaborate and carefully documented

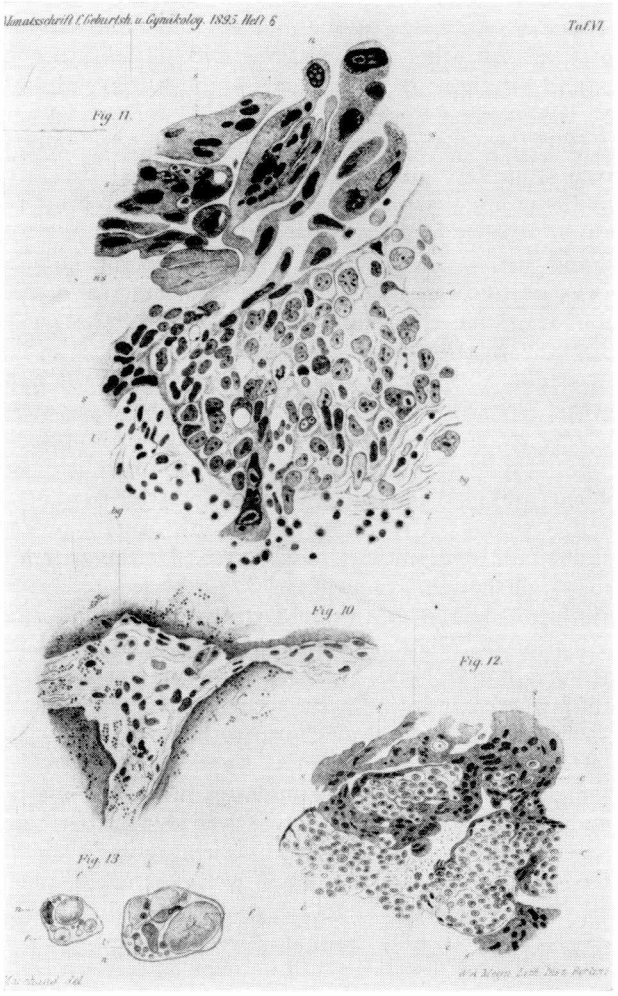

FIGURE 2. Reproduction of an illustration from Marchand's historical article.[1]

study was most influential in gaining acceptance for Marchand's ideas in the British Isles as well as in the United States (which had been previously prepared for this attitude by a case report by Williams,[11] a study somewhat less incisive than Teacher's masterful article). In 1907, Risel[12] summarized the question and supplied an extensive bibliography. By this time there were no serious challenges to Marchand's views.

Parenthetically, Schlagenhaufer[13] reported on cases of chorionepithelioma arising in testicular teratomas. Although he subscribed to Marchand's theory that chorionic elements were fetal in origin, he went too far, interpreting some of his observations as chorionic villi and fetal membranes within the teratomas. Risel[14] did not support this viewpoint in his authoritative monograph on the subject.

Once the tissue of origin was established, the next step was the taxonomy of the tumors and the other proliferations derived from it. Most of our current ideas and terminology stem from the influential publication in 1910 by Ewing.[15] His opening sentences are as valid today as they were then:

"When, in 1895, Marchand demonstrated that the 'deciduoma malignum' . . . is derived from chorionic epithelium and named this tumor 'chorioepithelioma,' it was felt that not only had important progress been made in the theoretical knowledge of this disease, but that the difficulties surrounding the diagnosis and prognosis of these growths would shortly be removed. The latter hope was destined to fail . . . It became more and more apparent that tumors of chorionic epithelium exhibit a wide variation in histologic structure, that the relation between histologic structure and prognosis is extremely uncertain, and that many curious features of the natural history of these growths, especially the spontaneous recovery of apparently hopeless cases, are wholly unparalleled by other malignant neoplasms. Today it may justly be said that the study of chorioepithelioma presents more peculiar problems and its diagnosis, prognosis, and treatment encounter more special difficulties than exist with any other known tumor process."

Ewing classified all chorionic proliferations under the general term chorioma, recognizing all the gradations of the lesion known today: hydatidiform mole, hydatidiform mole with trophoblastic proliferation, syncytial endometritis (syncytioma), chorioadenoma destruens, and choriocarcinoma (chorioepithelioma of Marchand). He employed these terms in substantially the sense that is currently in use. He recognized syncytial endometritis as equivalent to Marchand's atypical chorioepithelioma and defined it as an infiltration of the uterus with syncytial wandering cells which, although essentially benign, on occasion might simulate a tumor and merit the descriptive term syncytioma. On this subject he was in essential agreement with the previously stated views of Meyer.[16] Ewing coined the term chorioadenoma destruens, and likened the lesion to a destructive placental polyp, rarely if ever producing general metastases, reproducing in rather orderly fashion all the structures of a normal villus, although he conceded that extension into the broad ligaments and vaginal metastases could be found. He emphasized the point that more importance can be attached to the histological diagnosis of these tumors than is often claimed and that certain general relations between histological structure and clinical course can be established. Meyer's[17] full-length view of chorionic growths in 1930 shows that in two decades little of importance was added to the schema proposed by Ewing.

I do not propose to discuss these lesions individually; the pathological aspects are discussed in detail by R. R. Greene, W. W. Park, and N. B.

Friedman elsewhere in this monograph. As a pathologist, I can point out only the necessity for careful analysis and accurate diagnosis in individual cases. Novak and Seah[18, 19] report that, in addition to 74 cases of choriocarcinoma received by the Albert F. Mathieu Registry, Chicago, Ill., they also received 85 cases bearing this diagnosis incorrectly, an error of more than 50 per cent. Of the 85 misdiagnosed cases, 46 were hydatidiform moles with some degree of trophoblastic proliferation, 19 were examples of syncytial endometritis, and 15 were examples of chorioadenoma destruens. Novak and Seah state: "Malignancy as it occurs in trophoblastic lesions is determined by the microscope, as it is in all fields of pathology, and not by the clinical course. For example, if a trophoblastic neoplasm is microscopically and unquestionable choriocarcinoma, but the patient gets well, the honest conclusion is that some patients with this disease survive, and the incorrect one would be the cynical statement sometimes heard that the patient could not have had a choriocarcinoma just because she got well. One might just as well deny the malignancy of innumerable cervical cancers just because they were cured by treatment."

By the same reasoning, it can be pointed out that, although chorioadenoma destruens is not a malignant neoplasm in the sense that it will produce general metastases, some patients with this lesion will die because of hemorrhage, sepsis, or perforation. If the microscopic criteria of Novak and Seah are followed closely and if adequate sampling is made of tissue for microscopic study, the percentage of correct diagnosis in cases contributed to the Mathieu Registry would rise from less than 50 per cent to well over 90 per cent.

When we turn from a consideration of choriocarcinoma to its most frequent precursor, the hydatidiform mole, we are again in the debt of Marchand,[20] who in 1898 disposed of Virchow's concept that a mole was a myxoma of the stroma of chorionic villi. Marchand demonstrated that the changes in villous stroma are degenerative in nature, not proliferative, and that the feature of moles that gives them their distinctive clinical and pathological behavior is attributable to trophoblastic proliferation. Obviously, such a distinctive lesion as a hydatidiform mole could not have escaped recognition by the ancients. Actually, the term hydatid, meaning droplike, was first used by Aetius of Amida in the Sixth Century. In his recent monograph Smalbraak[21] has given a charming account of the delivery of the Countess of Henneberg on Good Friday in the year 1276, and it is not necessary for me to recount this singular episode. Our current ideas concerning the genesis of hydatidiform moles stem largely from the work of Hertig and Edmonds.[22] Elsewhere in this monograph Edmonds discusses both old and new concepts of the genesis of moles. I shall not encroach on his domain, but merely shall summarize a well-known point of view.

Hydatidiform degeneration of the stroma of chorionic villi is a quantifiable alteration, commonplace to some degree in almost every abortus, exaggerated in molar gestations. Transitional forms between ordinary abortuses and full-blown hydatidiform moles occur. In one sense a hydatidiform mole is a malformation of the placenta, a result of the failure of continuing fetal angiogenesis. The failure of a functioning fetal vascular system leaves the

trophoblast as a semipermeable membrane, and the physicochemical gradients favor accumulation of fluid derived from maternal plasma within the villous stroma. It is the accumulation of this fluid that produces the characteristic gross and microscopic features of the malformation. McKay *et al.*[23, 24] have shown by careful microchemical study that the fluid within molar villi represents a dialyzate of maternal plasma. Parenthetically, the traditional description of molar villi as avascular is not strictly true; on one occasion I laboriously examined 500 villi in each of 10 hydatidiform moles, a total of 5000 villi, and enumerated the number in which blood vessels could be detected. As I recall, capillaries can be seen in about 6 or 7 per cent of such villi, and an occasional vessel will contain a red blood cell. However, for all practical purposes, there is no fetal circulation and the villi are functionally avascular.

Inasmuch as the alterations in villous stroma are quantitative, the only place for qualitative change lies in the trophoblast, and the question of precisely when the qualitative change from hyperplasia to neoplasia takes place remains unanswered. If a mole is a tissue malformation in the sense of Nicholson, it has some increased facultative relation to tumor formation. Although we recognize this facultative relationship when trophoblastic proliferation is present, we are singularly ill-informed about the conditions that promote it. We have made but little progress since Teacher's statement in 1903: "I fear that, in spite of the intermediate stages between the mole and the tumor, we are not yet able to strip the mystery off the latter; we must infer that some unknown quantity has been added in those cases which develop into malignant growths."

Attempts to produce hydatidiform moles or chorionic tumors in animals bearing a hemochorial placenta have been as infrequent as they have been unsuccessful. Noyes,[25] who has been studying certain conditions that may influence trophoblastic proliferation, reports on them elsewhere in these pages.

For practical purposes, a number of attempts have been made to study and classify the degree of trophoblastic proliferation of evacuated molar tissue in an effort to predict which moles are more likely to eventuate into neoplastic lesions and which are likely to give no further clinical difficulty. Hertig and Sheldon[26] devised a six-point scale for classifying moles and were successful in segregating the innocuous from the dangerous. Unfortunately, they beclouded the issue by including their cases of syncytial endometritis and chorioadenoma destruens with the malignant tumors. However, their tabulations are so labeled that the reader may correct for this and still find a fair degree of correlation between the microscopic appearance of the trophoblast and its subsequent behavior. Some of Hertig and Sheldon's microscopic criteria will not find favor with contemporary microscopists, notably the criteria of "trophoblast invading its own stroma" and "tissue culturelike growth." However, Hertig and Sheldon are among the few writers in this day who use the term anaplasia correctly in its original sense, implying a morphologic reversion of the tissue in question to a more primitive stage in its ontogeny, and they are to be lauded for this. The grading of hydatidi-

form moles has become a somewhat controversial matter. Hunt *et al.*[27] have proposed a three-point scale of classification, and there is some evidence in a more recent publication by Hertig and Mansell[28] that these observers are currently using both systems. Needless to say, when one considers the large volume of tissue that a pathologist may receive from the evacuation of a molar pregnancy, the question of adequate sampling becomes important. The gross appearance of the vesicles and the accompanying mass of blood clot and debris does not assist in the selection of tissue for microscopic study; one must be prodigal with tissue embedded. There are occasional reports of the development of a choriocarcinoma or a chorioadenoma destruens following a mole in which little or no trophoblastic proliferation was seen; one always has the uneasy feeling that sections taken elsewhere in the tissue might have disclosed trophoblastic proliferation of a degree that would have given a clue to the subsequent course.

Novak and Seah[18, 19] place little confidence in the grading of hydatidiform moles in an effort to predict sequelae. Their attitude reflects, I am sure, the result of a sincere effort to apply the histological criteria used in both of the systems that have been proposed. When observers of considerable experience are in diametric opposition regarding the value of a method, the truth is likely to lie somewhere midway between the two extremes. Therefore, in my own laboratory we have adopted the French Impressionist maxim, "Hydatidiform moles are not black or white; they are varying shades of pink and blue." The entire controversy smacks of being a contrived issue.

Before leaving the subject of hydatidiform moles, I shall make two analogies that I have found convenient in practice. Syncytial endometritis following a molar pregnancy is an exaggerated reaction at the placental site, depending upon the presence of retained trophoblastic cells that have infiltrated portions of the endometrium; it is analogous to the changes seen in a postabortal or postpartum endometritis in which retained placental-site giant cells are found in the curettings. Exuberant trophoblastic proliferation is greater in many hydatidiform moles than in most aborted pregnancies and certainly greater than in term pregnancies; therefore, the amount of residual trophoblast (largely but not entirely syncytiotrophoblast) is greater and the reaction to it is more intense. Chorioadenoma destruens bears the same relationship to a molar pregnancy as placenta increta does to a term pregnancy. Incretion is more probable with a molar pregnancy than with a term pregnancy, again because of trophoblastic proliferation.

Any future increase in our understanding of the behavior of trophoblastic lesions will depend upon our awareness of the fundamental biological properties of trophoblast and its products. Elsewhere in this monograph B. G. Böving discusses some of the biological properties of trophoblast and implantation; J. T. Velardo, the endocrine action of chorionic gonadotrophin; and E. Delfs, the application of quantitative studies of this hormone in problems of clinical diagnosis and management. I regret that both space and the state of our present knowledge do not permit a discussion of the steroid hormones also elaborated by the placenta.

I must comment briefly on a few of the aspects of trophoblast that have

both fascinated and baffled me. These are the interrelated problems of invasion, transport, immunity, and regression.

With respect to invasion, the affinity of trophoblast for maternal blood vessels has been noted since observers first trained their microscopes on the placental site, on trophoblastic tumors, and on the lungs of women dying during pregnancy (FIGURE 3). Invasiveness is not a property confined to neoplastic trophoblast as it is to other epithelia, unless we consider all placental tissue as a new growth; it is a property of normal trophoblast. The mechanism of invasion remains obscure. One reads remarks about the proteolytic activity of trophoblast. Is this hypothetical proteolysin an

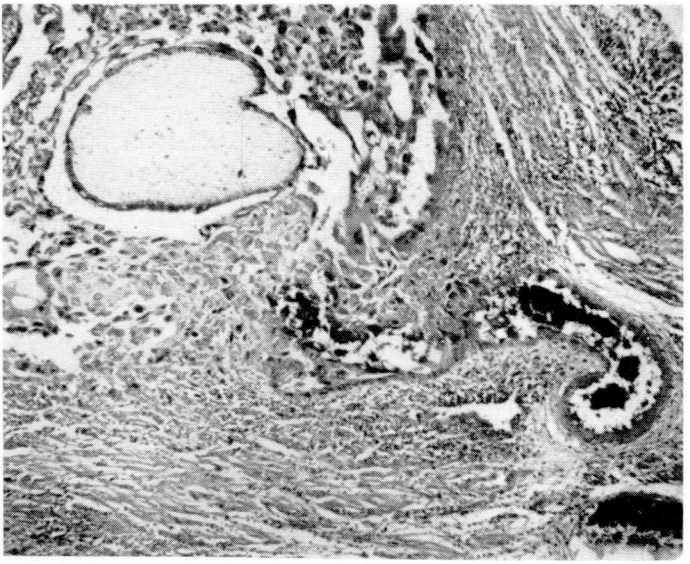

FIGURE 3. Chorioadenoma destruens showing a molar villus with proliferated trophoblast invading a vein deep in the uterine wall.

enzyme? If so, upon what specific substrate does it act? Is its action controlled or modified by any or all of the hormones elaborated by the tissue? Does it act upon maternal cells or upon the intercellular ground substance in the decidua or in blood vessel walls? It is one thing to hypothesize an enzyme; it is a different thing to isolate it. We have reached a stage of sophistication in enzymology that no longer permits us to postulate enzymatic activity with the same ease that a family doctor tells a patient that he is suffering from a virus. Unfortunately, none of the enzymes isolated so far from placental tissue appears (insofar as tested) to facilitate invasiveness. Gey and his associates[29, 30] were able to grow trophoblast in tissue culture and demonstrate elaboration of chorionic gonadotrophin into the nutrient medium. Waltz *et al.*[31] demonstrated gonadotrophins by culture of tissue from an hydatidiform mole even after a year of continuous growth. However, there has been no satisfactory investigation of enzymes elaborated by

trophoblast in tissue culture. Leighton's recent review[32] of the contributions of tissue culture to oncology indicates that there is considerable activity in the application of this technique to the study of invasiveness by tumor cells, but to date nobody seems to have investigated the invasiveness of non-neoplastic trophoblast.

The consequence of invasion is transport. It is not difficult to visualize how trophoblastic cells that have invaded maternal blood vessels are transported to the lungs and elsewhere. This phenomenon is called physiological deportation when it involves nonneoplastic trophoblast and tumor embolization when it involves choriocarcinoma. The German term, *Verschleppung*, is particularly apposite. Schmorl[33, 34] was able to find *verschleppte* placental cells in the lungs of 80 per cent of 158 women dying during pregnancy from a variety of causes. His observations were essentially confirmed by Veit[35] and Poten[36] who observed fragments of chorionic villi as well as isolated syncytial cells in the pulmonary vascular bed. Parenthetically, the diagnosis of deported trophoblast depends upon the demonstration of syncytiotrophoblast, not only because most of the material studied dates from the last trimester of pregnancy when cytotrophoblast has all but disappeared from the placenta, but because it would be extremely difficult to identify with certainty an isolated cytotrophoblastic cell in a pulmonary capillary.

The fate of transported trophoblast has been debated sporadically since the turn of the century. Most contemporary observers concur with Dunger's[37] opinion that, for the most part, *verschleppte* trophoblast in normal pregnancies survives for a limited period and then undergoes autolysis. However, trophoblastic emboli from hydatidiform moles may persist and even proliferate, elaborating enough gonadotrophin to produce a continuing positive bioassay. It is conceivable but difficult to demonstrate that such embolizations may remain latent for a period of time, eventuating in either a primary choriocarcinoma of the lung or in multiple metastases of choriocarcinoma with no evident primary site in the uterus. The circumstances under which such neoplastic transformation may occur remain undefined.

Precisely how long deported trophoblast can remain in the pulmonary vascular tree is debatable. I have studied material* from the case of a 19-year-old girl who died of subacute bacterial endocarditis with a terminal subarachnoid hemorrhage. One month prior to admission for her terminal illness she had undergone curettage for an incomplete abortion. The medium-sized and small arteries at the pulmonary apex contained viable clumps of proliferated trophoblastic cells, and there was surprisingly little cellular reaction to their presence. A few scattered trophoblastic cells were present in the regenerated endometrium as well. No trophoblast was detected in the area of cerebral hemorrhage.

A fatal outcome may ensue from embolic trophoblast that has not invaded the pulmonary parenchyma[38, 39] if the embolization is extensive enough to produce sufficient pulmonary arterial obstruction to create either acute or chronic cor pulmonale. Harrison[40] has demonstrated this phenomenon and, through his courtesy, I have received further details of the clinical history

* Courtesy of Harold Lepow, Lincoln Hospital, New York, N. Y.

and duplicate pathological material (FIGURES 4, 5, and 6). The patient was a 47-year-old woman whose youngest child was 11 years old. Three months before admission she had aborted spontaneously and her menses had not resumed. She developed signs and symptoms of acute right-sided heart failure and pulmonary hypertension and died one month later. Autopsy disclosed that the lungs were studded with whitish plugs of embolic trophoblast. Similar emboli were found in the left ovarian vein and the paracervical venous plexus, but no residual trophoblast was found in the uterus itself. Despite careful search, at no point was invasion beyond the blood

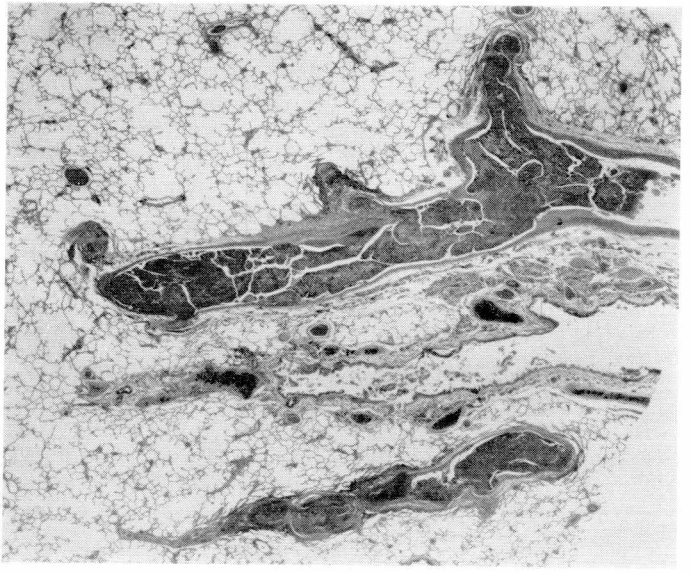

FIGURE 4. Choriocarcinoma embolic to lung without parenchymal invasion. Large branches of the pulmonary artery are filled with embolic tumor creating pulmonary hypertension and leading to death in cor pulmonale. Reproduced by permission from C. V. Harrison.

vessels found in this case of choriocarcinoma. The walls of some of the pulmonary vessels harboring embolic tumor were diffusely infiltrated by inflammatory cells, somewhat reminiscent of an allergic arteritis.* Also, I was privileged to study a similar case with Hugh Grady at the Armed Forces Institute of Pathology, Washington, D. C. in which the pulmonary arterial obstruction was in the form of a large thrombus in the main pulmonary artery, its major rami not extending into the smaller vessels of the lesser

* Between the date of compilation of the monograph and the time of publication, K. D. Bagshawe and W. D. W. Brooks reported on "Subacute pulmonary hypertension due to chorionepithelioma" (Lancet **1**: 653–658, March 28, 1959) citing this case in detail as well as one other autopsied case and one case with survival following methotrexate therapy. In these 3 cases there was no evident tumor in the endometrium, but there was extensive embolization to the lungs.

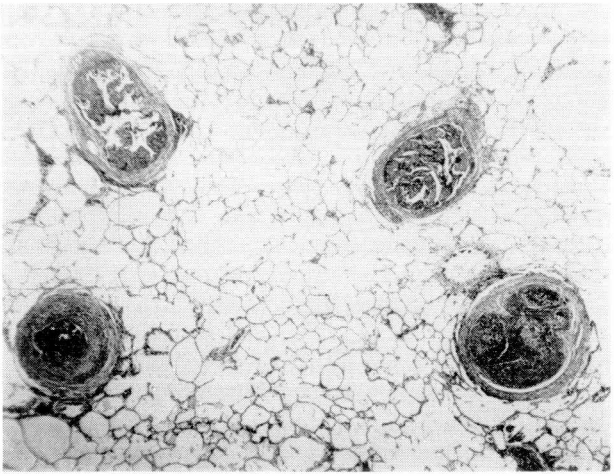

FIGURE 5. Same case as shown in FIGURE 4. Cross section of medium-sized pulmonary artery branches show the diffuseness of the embolic process. The walls of all four vessels are thickened and inflamed.

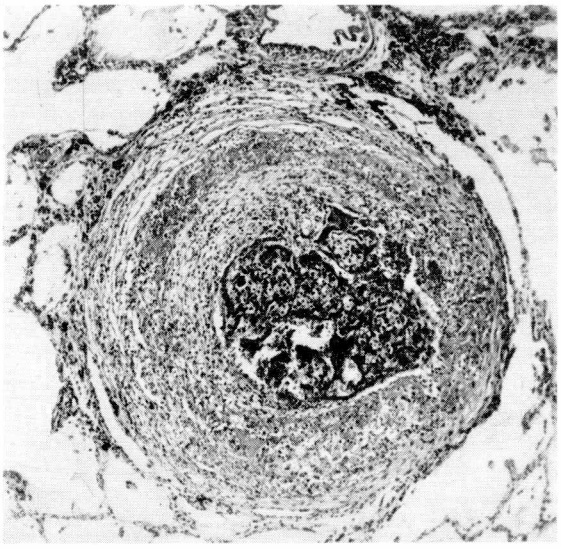

FIGURE 6. Same case as shown in FIGURES 4 and 5. Detail of a pulmonary artery branch containing embolic tumor. The entire thickness of the vessel wall is infiltrated by lymphocytes and plasma cells. In the ground substance of the media there is amorphous eosinophilic material suggesting fibrinoid.

circulation. Obstruction was incomplete and the clinical course was prolonged. On gross examination, the thrombus appeared to consist entirely of clotted blood; only on microscopic examination was it apparent that relatively small amounts of trophoblast were present near the intimal surface and that over a period of time layer upon layer of clotted blood had been deposited upon the trophoblast. Subsequent to this observation it was discovered that the patient's last-known conceptus had been more than two years prior to her death.

Recently, Park[41] has investigated the results of intravenous injections of an emulsion of homologous and autologous placental tissue in mice. The injected material behaved as bland emboli with no significant inflammatory reaction, no real organization. Park[42] has described an example of embolic decidua in the lung of a pregnant woman, and Lattes *et al.*[43] have reported an example of pulmonary endometriosis with decidual transformation of the stroma. The latter case occurred during the patient's second pregnancy and was interpreted as the result of embolic displacement at the time of cesarean section at the end of her first pregnancy. It is interesting to speculate on the possibility of embolic trophoblast implanting on previously embolized and viable decidua. Yet no one has successfully injected trophoblast intravenously and succeeded in making it "take." In this respect Park's results are as negative as those of Maximow (1898) and Lengemann, (1899) both of which he cites.

The question of immune responses by the maternal organism in response to the presence of trophoblast remains largely a matter for speculation. It is possible to record a long list of experimental failures starting with the pioneer work of Scholten and Veit[44] and their syncytiolysin. Elsewhere in this monograph W. A. Bardawil and B. L. Toy discuss this problem in detail. One of the chief difficulties encountered is that most of the substances prepared for experimental study have been toxic. This inevitably raises the question of the relationship of trophoblastic lesions to toxemias of pregnancy. It is readily established that there is a higher incidence of toxemia in molar than in nonmolar pregnancies. However, in the few recorded instances in which frank choriocarcinoma existed concomitant with an otherwise normal pregnancy, there has been no conspicuous evidence of toxemia. Despite the fact that immune substances have yet to be isolated from trophoblast, Schopper and Pliess[45, 46] have drawn the analogy between the behavior of choriocarcinoma and inoculation tumors, and Schuster[47] has expanded the analogy to include tumor induced by filtrable viruses.

As a morphologist, I am tempted to think that most efforts to investigate this problem have been misdirected. In these days when there has been so much interest in tissue transplantation, I can suggest merely that the fertilized-ovum implanting is a naturally occurring instance of transplantation, a structure that is half homograft and half autograft (half autologous and maternal, half homologous and paternal). Under normal circumstances its behavior is quite predictable and quite suitable for experimental investigation. I also suggest that the placental site has the anatomic hallmarks of a field of immune tissue response. Such phenomena as fibrinoid, alteration