TUMORS of the PLACENTA and UMBILICAL CORD

Shanklin

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With a foreword by

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Tumors of the Placenta and Umbilical Cord

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FOREWORD

Humani generis mores tibi nosse volenti
sufficit una placenta . . . .
After Juvenal*

The intermediary organ of mammals in development, that standing between the mother and the individual, at once the "other" of the unborn infant and containing a trace of the mother, has recently become of increasing interest to medical scientists. The immunological role of this organ, its extraordinary ability to synthesize enzymes and hormones, its selective competence in transporting nutrients, drugs of abuse, environmental toxins, and other substances, not to mention a variety of microorganisms, make the placenta unique in its biological universe. This short lived organ is beginning to become the focus of research in trophoblast surface receptors, research that suggests additional facilitative abilities in the face of challenges, internal and external.

In 1956, Arthur T. Hertig and Hazel Mansell (Gore) prepared the "Tumor Atlas on Hydatidiform Mole and Choriocarcinoma" for the Armed Forces Institute of Pathology Atlas Series. In the classic texts on human placental pathology by Benirschke and Driscoll, Fox, and more recently in my "Pathology of the Placenta," as well as in standard works on gynecological and obstetrical pathology, are brief, informative discussions of neoplasms of the placenta and umbilical cord.

What is now needed and what is presented in Dr. Shanklin's text is a hybrid out of the "Hitchhiker's Guide to the Galaxy" and a textbook on the philosophy of evidence. The peculiar nature of normal, dysfunctional, near neoplastic, and neoplastic trophoblastic proliferation offers difficult diagnostic challenges to the practicing pathologist. As in most neoplastic problems, the most exact diagnosis will usually yield an agreed upon mode of therapy. The changing nature of the language of diagnosis of trophoblastic disease has made rigid protocols all but impossible. Fortunately, follow-up after initial diagnostic biopsy has been enhanced by quantitative endocrine chemistry and immunocytochemistry. The rare primary tumors of placenta and cord offer biological challenges and metastatic neoplasms in placenta from both fetal and maternal sources present intriguing puzzles as to primary origin.

The wide experience and careful scholarship of the author is aided by the felicity of the language, so necessary in a dense package such as this monograph. Unexpected outcomes of vascular disorders of both placenta and cord, from congestive failure through failure to thrive and intrauterine growth retardation associable with chorangiomas to near fatal bleeding as a result of ruptured cord angiomas, make the benign tumors equally intriguing. The biology of molar and "partial" molar villous disease has become one of great theoretical and practical importance. The same can be said of the

surprising, if uncommon, propensity of choriocarcinoma to involute spontaneously or after less than complete therapy. The future will yield more treasures from the dragon's hoard of placental pathobiology, more than hinted at in the author's epilogue.

We have just begun to tap the vital humors of this "shadow" ("I have a little shadow that goes in and out with me, and what can be the use of him is more than I can see . . . "—Stevenson). We pathologists, participant observers in our mortality and our growing expert knowledge of the placenta, well know what use it is.

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* If you would study the ways of the human race, one placenta is enough.

PREFACE

On January 3, 1956, at Duke University Hospital, I began my first systematic study of placentas. As it happens, 1956 was an auspicious year for placental studies because of the publication of the fascicle on trophoblastic tumors by Hertig and Mansell. I acknowledge stimulation from Arthur T. Hertig and his work, which was a pioneering American effort to understand implantation and early events in placental development. The Hertig-Mansell work has not been replaced in that series; possibly this book would serve as a bridge from their mid-20th century understanding to a much different 21st century tumor biology, of which trophoblast stands as one of the earlier spans.

Whereas earlier emphasis has been almost exclusively limited to tumors of trophoblast, this work is balanced by detailed consideration of the mesenchymal tumors of placenta, known generally as chorangiomas, and of metastatic neoplastic lesions from both maternal and fetal sources. Certainly the literature of the past 33 years has been a rich one for chorangioma. I found my first example with Duke Hospital placenta number 216, just seven weeks into the work.

Books like this are assembled by accretion, as one avenue of consideration or line of questions leads to another, culminating at a time when all seems complete except for the necessary revisions based on helpful reviews and the forced re-examination brought about by the act of writing an index. The initial step is found in pathological training. My mentor, the late Wiley Davis Forbus, founding chairman of pathology at Duke, was a natural historian of the 19th century school when it came to understanding the relation between lesions and their functional effects which are expressed in clinical ways in the human species. This bias is heavily reflected in this work. It represents a point of view which I believe is critical to the future of tissue pathology. The ultimate test of a neoplastic process is not the patterns used commonly for diagnostic classification, but the effect the process has on the patient-host. Given the emphasis on functional interpretation of tissue lesions at Duke during 1930 through 1958 it is of interest that much important American work on trophoblastic disease of the 1970s and 1980s has also come from that institution.

My initial work was done under the approval and strong encouragement of the late Francis Bayard Carter, founding chairman of obstetrics. Dr. Carter thought I should deliver some placentas myself and so, over a six month period, I may have been the only pathology intern in the country to deliver 25 or so infants and placentas. I owe especial thanks in those early days to Dr. Roy Turnage Parker (who followed Dr. Carter as chairman), Dr. Walter B. V. Cherny, and Dr. Bernard F. Fetter. Dr. Cherny was especially helpful after I left Duke as he researched a number of clinical charts for me. Since the project led directly to meeting the future mother of my children, Dr. Cherny helped again by delivering two of them, adding satisfactorily to the placental collection!

Particular thanks are due Dr. Charles B. Hammond, present chairman of the Duke department of obstetrics, for valuable time generously given and his many letters

explaining new points on the clinical diagnosis and treatment of gestational trophoblastic tumors.

Increased skill in observation requires better records and vice versa. By the time the work moved to the University of Florida in 1960, a protocol had been developed. These records remain useful in large part because of the efforts of the late June L. Rutan, my secretary there for four years, and to several of my student fellows. Dr. Perry A. Berman and Dr. David A. Cimino made the most lasting and valuable contributions. Mr. Lewis Hayes and Mr. Robert Sleight served as technical assistants for several years. It was during this period that I began lasting professional relationships with Professor Cirilo Sotelo-Avila and Professor Frank G. Crussi, originally for them as fellows. They have made material contributions to my personal collection over the last 25 years. Gerold L. Schiebler, Professor of Pediatrics in Gainesville, Florida, arranged for review of some clinical charts specifically to flesh out my records on several cases for this book.

In 1967, the project moved to the Chicago Lying-in Hospital. Dr. Frederick Paul Zuspan, then chairman of obstetrics at the University of Chicago, provided an environment conducive to scholarly research and effective cooperation between clinicians and pathologists. Dr. Luis A. Cibils and Dr. Atef Moawad were especially supportive. The laboratory of developmental pathology was part of the department of obstetrics. My close associate of nine years, the late Dr. John Roosevelt Esterly, made many valuable suggestions and provided friendly but quality criticism at many points. The assembly of information for writing about placentas began in Chicago. This was aided by making placental examination part of the basic laboratory service. I was assisted by Mrs. Elema Wilson and Mrs. Yolanda Ashby with respect to records. Technical matters were handled most ably by Miss Maureen H. Boo. High skills in histopathology were exercised by Mrs. Gladys McJulien, Mrs. Blandyna Szezesniak, Miss Laura Regut, and Miss Manula Karman. The John A. Hartford Fellow in Perinatal Pathology, Dr. Katherine Kyriazis, exemplified the meticulousness needed for effective study of the placenta. Our special 1973 fellow in placentology, Dr. Virginia J. Baldwin, made many additional contributions, not the least of which was some ten years later when she served as a reviewer of the first draft of this book. Dr. Catherine Dobson of the private service at Lying-in provided me with several examples of late placental site changes.

At this point I was asked by Dr. William H. Hartmann, then chairman of pathology at Vanderbilt, to consider a formal work on the specific subject of placental tumors. He was especially helpful in arranging for six different trips to the Armed Forces Institute of Pathology during 1978 and 1979 to review their collection on placentas and placental tumors and to obtain illustrations. This arrangement was aided by the avid cooperation of Dr. Henry J. Norris and Col. William R. Cowan, then deputy director. The fruit of their assistance is throughout this book. Bill Hartmann, a medical classmate of mine, later reviewed both the first and second drafts.

Many helpful persons are expressly acknowledged at various points in the work, but others are best thanked here: Dr. Richard Gorenberg and Dr. Donald S. Menzies, for clinical information; Dr. Ralph M. Wynn for help in contacting others; Messrs. Edwards, Allen, and Wilson of the AFIP photographic department; the staff at Light Work (photo)

Labs, in Gainesville; and for case material, Dr. Robert H. Koehl and Dr. Abolghassem Hatef, Cheverly, Maryland; Dr. Robert E. Klein, Gainesville; Dr. Alvan G. Foraker, Jacksonville, Florida; Dr. A. William Carlson, Reno, Nevada; Dr. Avery L. Cook, Lake Charles, Louisiana; Dr. Donald D. McNeill, Morganton, North Carolina; Dr. David L. Bowerman, Colorado Springs, Colorado; Dr. Russell G. Lindauer and Dr. J. Frederick Rommel, Oneida, New York; Dr. David B. Jones and Dr. John T. Prior, Syracuse, New York; and Dr. G. K. Missen and Dr. J. B. Blaikley, Guy's Hospital, London, England. Dr. Peter Gruenwald, to whom I have dedicated this book, graciously shared much material with me and gave me encouragement over many years. I regret he did not live to see the first full text draft, as I would have wanted his opinion on it.

A particular word of thanks to my colleague and good friend, Professor James S. Scott of the University of Leeds, England, for the long-term loan of his personal copy of K. D. Bagshawe's book, *Choriocarcinoma* (1969).

The initial draft was begun in earnest in 1981 during that period when I was a non-university based consultant pathologist. My Florida based staff, Mrs. Susan B. Harrison and Mrs. Marion E. Freeland, turned scribble into text, and Mrs. Freeland made the medical library of the University of Florida her second home, an activity which has continued to the present. The second major draft was completed in 1983 and would have been impossible without their dedication. The third and final phase of writing and development began in the summer of 1988 through the device of an epilogue to bring matters up to date and to point more vigorously toward the future.

The immediate family of writers of books, of whatever kind, are often exposed to the clutter of papers and reference cards (and in the final draft, to computer diskettes) and to the eccentricities by which concentration is sometimes viewed. As I know nothing of the placentas of myself or their mother (a singular failing of most placentologists I would aver) it would be best to close by noting the tolerance and encouragement of five persons from my collection of over 25,000 placentas: Elizabeth, Leigh Dabney, Lois Virginia, John Carter, and Eleanor. May the strength of their implantation augur well for their futures.

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Chicago, Illinois

Dedicated to the memory of

Peter Gruenwald, M.D.

1912–1979

Embryologist, developmental pathologist,
placentologist extraordinare

CONTENTS

Some understanding of early placental development is useful in any consideration of tumors of the organ.

The future shape of the discoid placenta is not visible in the early implantational stages. The earliest stage seen by this author was about 10 days postconceptional, that is some 2 or 3 days postimplantation (fig. 1). The trophoblast was a loose aggregation of cells resembling tissue culture explants. The trophoblast was seemingly random, with many open spaces and an irregular hemorrhagic zone at the interface with the endometrial stroma. Delamination of prototrophoblastic cells from these anchors serve as the placental mesenchyme. This gives rise to angioblasts, fibroblasts, and placental reticuloendothelial cells. Just after this same period, generally, but in some areas earlier, the distinction between cytotrophoblast and syncytiotrophoblast becomes apparent

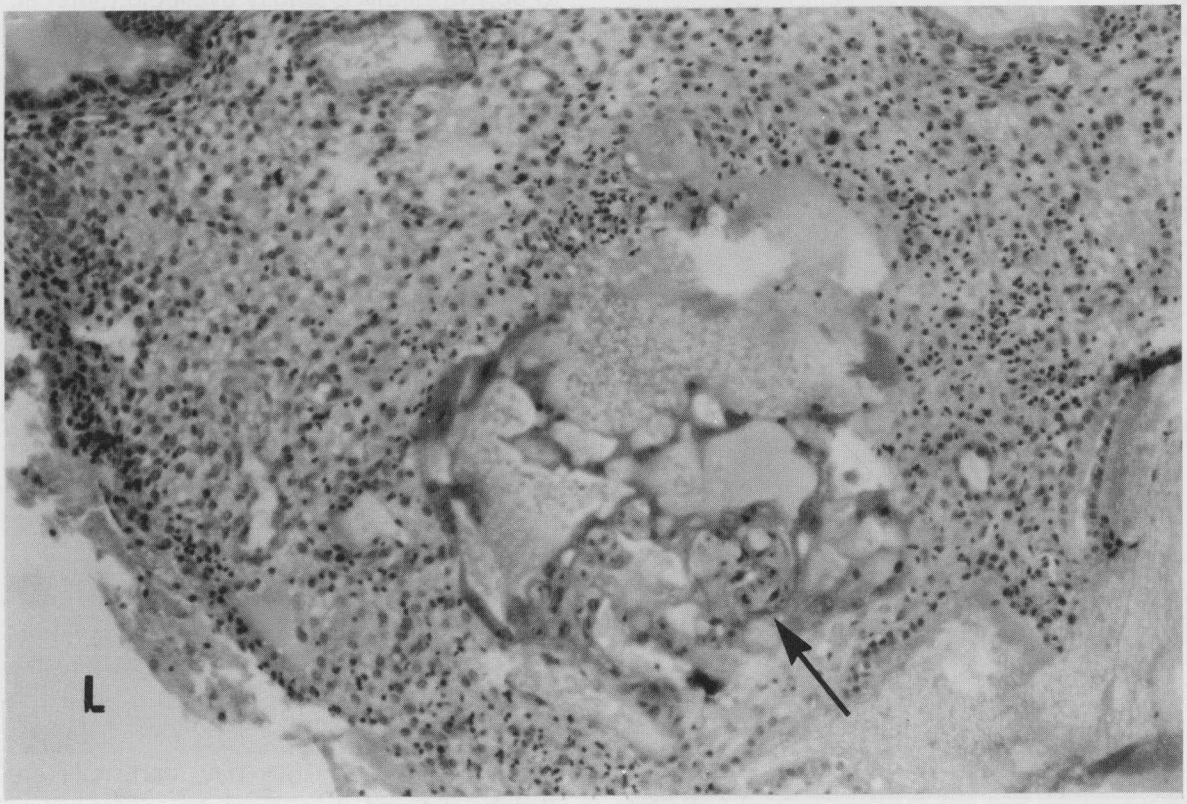

Figure 1
EARLY IMPLANTATION

About 10 days postconception and perhaps 2 or 3 days postimplantation. Note lack of subsurface laminar decidua adjacent to endometrial lumen (L). The early trophoblast is mainly an irregular cellular bridging of a blood lake which seems to be continuous with the stroma (middle zone). The more dense cell mass in the lower half of the field (arrow) appears to be cytotrophoblast rather than embryonic primordium. Inflammatory nuclei in stroma, while seen at stages of endometrial development just beyond this, can be found on cycle day 24 by careful search. Nevertheless, these seem more numerous than expected; they also tend to encircle the implanted trophoblast. Hematoxylin and eosin stain.* X100.

*Throughout this book where the stain is not designated, hematoxylin and eosin stain has been used.

(fig. 2). The open spaces or lacunae eventually coalesce into the intervillous space, with communication to the maternal vascular system at the sites of hemorrhagic leaks. This previllous stage is seen generally around the inner cell mass, the future embryo showing both axial and orientational differentiation, which is smaller than the trophoblastic mass.

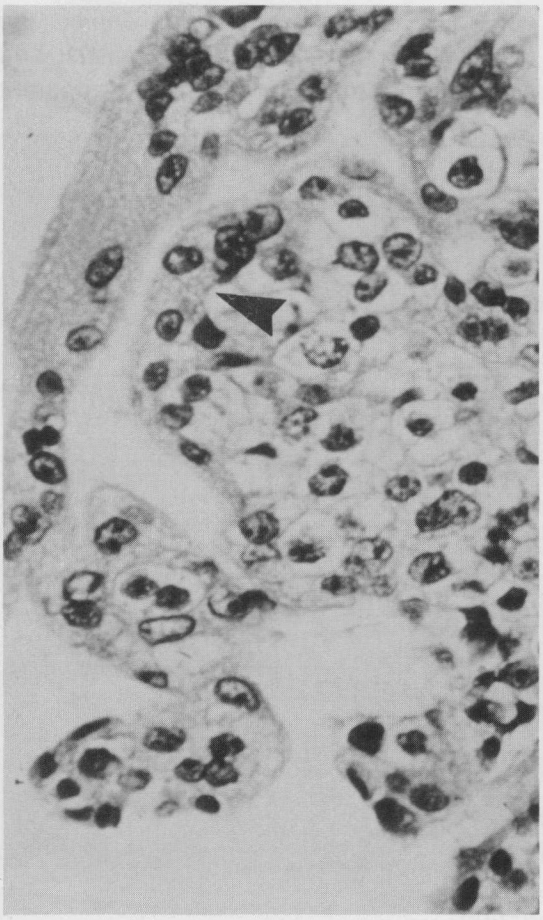

Figure 2
TROPHOBLASTIC NODULE
Cytotrophoblastic nodule with superficial syncytiotrophoblast. Note especially the degree of variability of the cytotrophoblast nuclei. Near the crescent in the upper left is a small zone of syncytial cells (arrow) within the contour of the nodule (? arising from). X200.

HISTOGENESIS

Trophoblast

Soon after fertilization, the primitive blastocyst differentiates into an inner cell mass and the outer trophoblast. The zona pellucida disappears and implantation occurs. During implantation there is further differentiation into cytotrophoblast and syncytial trophoblast. The cytotrophoblast is that which immediately surrounds the mesenchymal core of the villi. It is composed of fairly large pale-staining cells with prominent vesicular nuclei. Mitosis is scant to absent in most readily available material.

Specimens approximately 8-10 days of postconceptual development represent the earliest stages of development of trophoblast so far studied. Hertig and Mansell showed a 7.5 day specimen in which the trophoblast was solid, but contained both primitive syncytial and cytotrophoblastic elements (fig. 3). By 9 days, the primitive syncytial trophoblast is more abundant and displaced to the periphery. Some illustrations show vacuolation of trophoblast. By contrast, the cytotrophoblast tends to surround the chorionic cavity, forming small masses thought to represent prototypical villi (fig. 4).

By the 11th and 12th days, with prototypical villi more obvious, some coalescence of the vacuoles in the syncytial trophoblast suggests the future intervillous space (figs. 5, 6).

By the 14th to 16th day, early villi are clearly defined and irregular cytotrophoblastic columns extend from the floor of the developing placenta to the chorionic membrane. Syncytial trophoblast coats the cytotrophoblast of primordial villi. The intervillous space is completed by coalescence of vacuoles in the syncytial trophoblast and

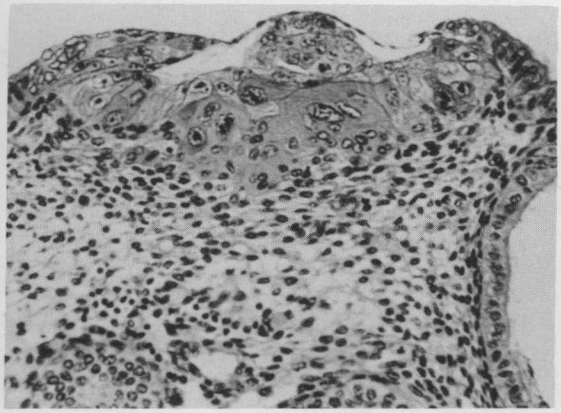

Figure 3
EARLY IMPLANTATION

Midzone cross section, normal 7.5-day human blastocyst. The trophoblastic plate in contact with the endometrial stroma is thick. Note thin, horizontal blastocyst cavity. Darker multinucleate syncytiotrophoblast is mingled with larger clear cytotrophoblast. Small ovoid embryonic mass is two layers thick (in blastocystic cavity). Note attenuated cellular "roof" to the cavity in continuity with the lateral trophoblast. X175. (Fig. 14 from Fascicle 33, Part 1, First Series, Atlas of Tumor Pathology, 1956.)

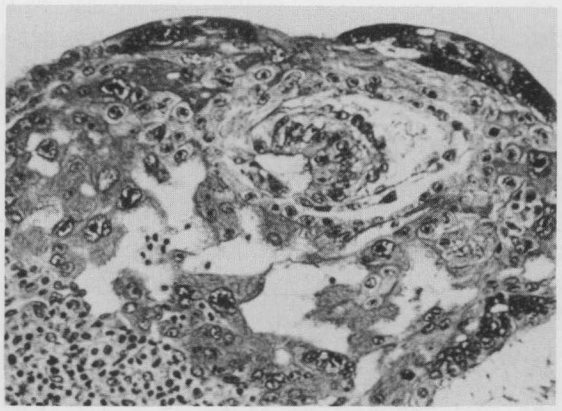

Figure 4
EARLY IMPLANTATION

Midzone cross section, normal 9-day human blastocyst. Note enlargement of field of trophoblast, now showing coalescence of vacuolar spaces. More precise zonation of trophoblast with syncytial cells mostly peripheral. Blastocystic cavity, now lined by definable chorion, contains an embryonic mass larger than in figure 3, with axial and spatial orientation. X175. (Fig. 15 from Fascicle 33, Part 1, First Series, Atlas of Tumor Pathology, 1956.)

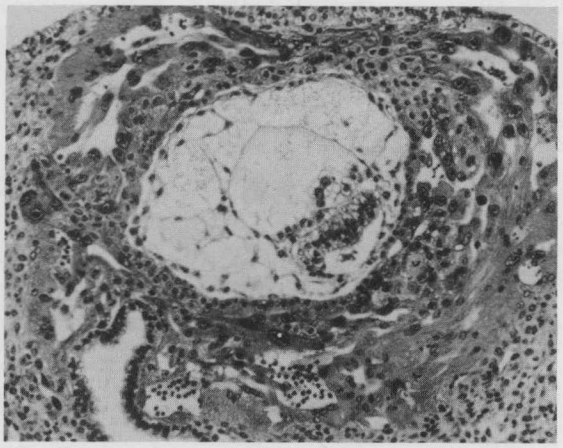

Figure 5
EARLY IMPLANTATION

Midzone cross section, normal 11-day human blastocyst. This is marked by further differentiation of the trophoblast rather than growth of outer dimensions. The chorionic cavity is well shown. Nodular aggregation of cytotrophoblast denotes the cellular cores of future primary villi. Amnion is delaminating from the cellular chorion. A yolk sac is attached to the embryonic disc. X100. (Fig. 16 from Fascicle 33, Part 1, First Series, Atlas of Tumor Pathology, 1956.)

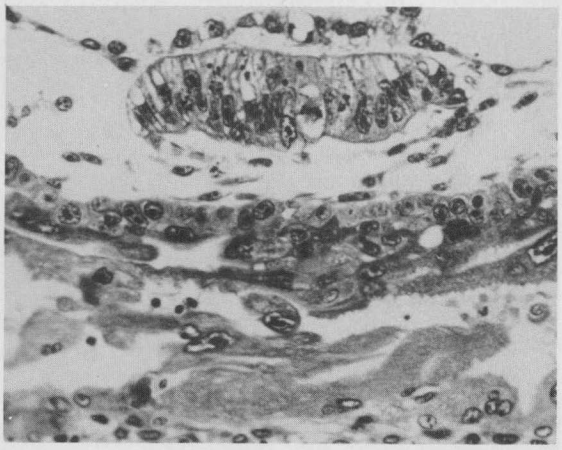

Figure 6
EARLY IMPLANTATION

Midzone cross section, normal 12-day human blastocyst. There is a bilaminar germ disc, an inner cytotrophoblastic layer, a thick outer syncytiotrophoblastic layer, and maternal blood in the coalescing vacuolar spaces. The latter is the precursor of the intervillous space. Cytotrophoblast is now a single layer except at the nodules, the villous precursors. X250. (Fig. 17 from Fascicle 33, Part 1, First Series, Atlas of Tumor Pathology, 1956.)

the essential relationships of future placental development are established. Portions of maternal blood may now be seen in the space between villi (figs. 7, 8).

Histochemical stains have demonstrated a variety of materials made or stored in trophoblast (McKay et al.), including chorionic gonadotropin (de Ikonicoff and Cedard). A PAS-positive basement membrane is laid down between these cells and the mesenchyme. Outside the cytotrophoblast is a syncytial layer of variable nucleation. No cell boundaries are seen here, but the boundary with the cytotrophoblast is distinct. The syncytium is commonly vacuolated. Histochemical technics have suggested that the steroid hormones of the placenta are made here (Ryan). In time, fewer cytotrophoblastic cells can be recognized by light microscopy (Fox, 1978). A roughly reciprocal relation exists between the decline of the cytotrophoblast and the growth and expansion of the syncytial layer. Pierce and Midgley have shown that syncytiotrophoblast has its origin in the cytotrophoblast. During the third trimester, syncytial nuclei tend to cluster and assume a polypoid profile called "knots" (fig. 9). In some term placentas this is striking, and the extent of anucleate bare cytoplasm is often astonishing.

An intermediate form of trophoblast with distinctive immunocytochemical features has been described both in placental sites and in trophoblastic tumors (Kurman et al., 1984). Syncytium contains both placental lactogen (hPL) and chorionic gonadotropin (hCG), cytotrophoblast is largely devoid of both (except in choriocarcinoma), and intermediate trophoblast contains mostly hPL.

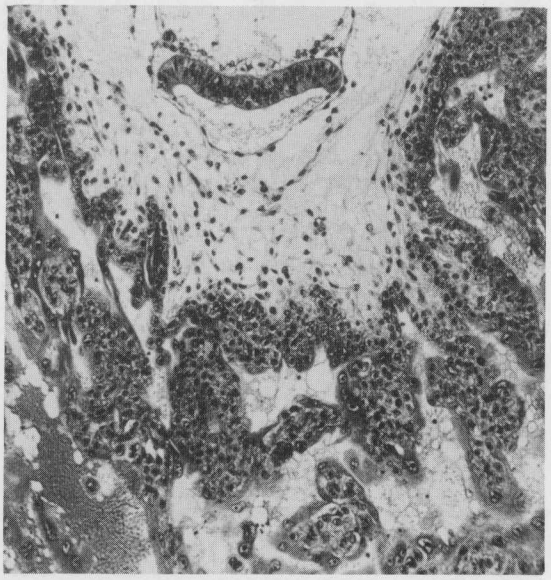

Figure 7
EARLY IMPLANTATION
Midzone cross section, normal 14-day human blastocyst. Primitive chorionic mesoblast is now evident and villi assume an arborized outline. The trophoblastic lacunae are more confluent and definite. X100. (Fig. 18 from Fascicle 33, Part 1, First Series, Atlas of Tumor Pathology, 1956.)

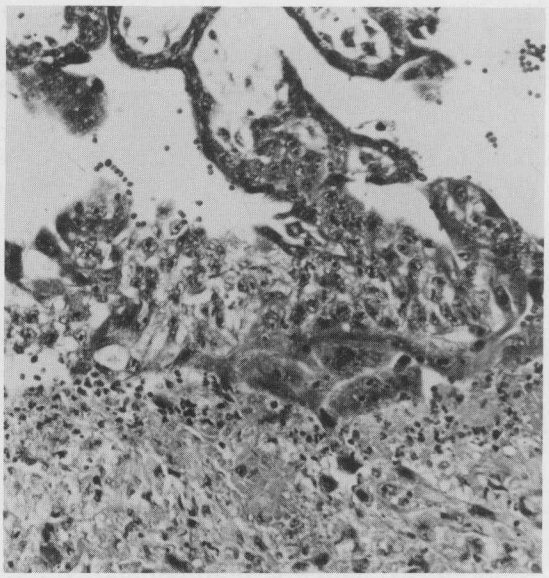

Figure 8
EARLY IMPLANTATION
Implantation pole (site) of a 14-day human blastocyst; curettage specimen (lactating woman following a prior normal pregnancy). Essentially solid cytotrophoblast at core of primordial villus is continuous with similar tissue on the floor plate. Syncytiotrophoblast covers the villi. X150. (Fig. 19 from Fascicle 33, Part 1, First Series, Atlas of Tumor Pathology, 1956.)

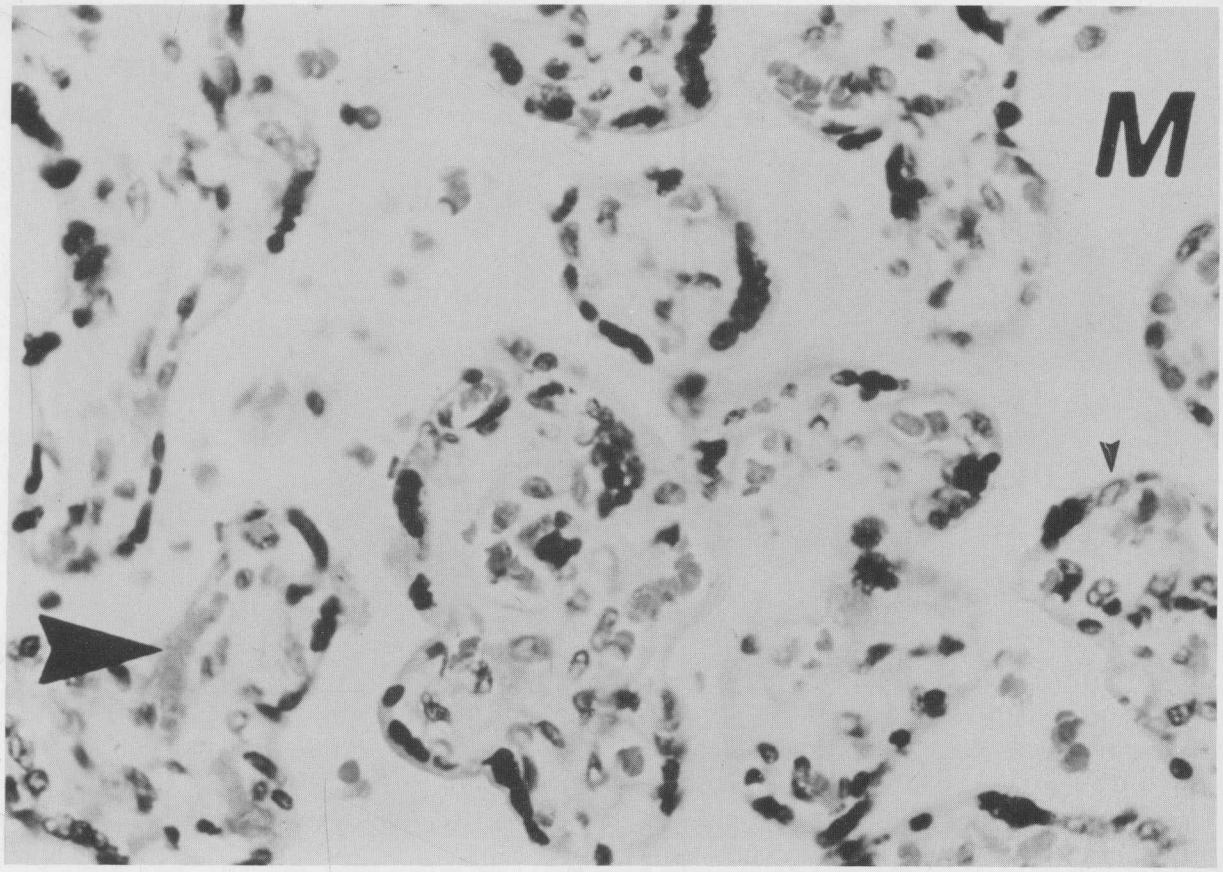

Figure 9
MATURE PLACENTA

Late third trimester tertiary villi. A few maternal erythrocytes are in the intervillous space (M). Note tendency for syncytial nuclei to cluster into "knots." Occasional bare cytoplasm (large arrow) is near these clusters, a point suggestive of nuclear migration. These bare zones erode sometimes with fibrinoid deposit occurring at that point. Persistent cytotrophoblast is present at term, but is hard to find, especially in formalin fixed material (small arrow). Note frequent direct capillary-trophoblast contact, also known as vasculosyncytial membrane formation. X400.

Stroma

An early derivative of the trophoblast, the stroma, forms the connective tissue cores of the villi, stems, and stalks. In so doing it also gives rise to the villous vascular system and probably also to the reticuloendothelial system or macrophages, known in villi as Hofbauer cells. The basic stromal cell has a small darker nucleus with ill-defined cytoplasmic boundaries, sometimes fusiform, sometimes stellate (fig. 10). In the mature villus, a distinction cannot always be made between the resting macrophages and the stromal cells. While not proof of their interconversion, this common observation at least begs the question of their relationship.

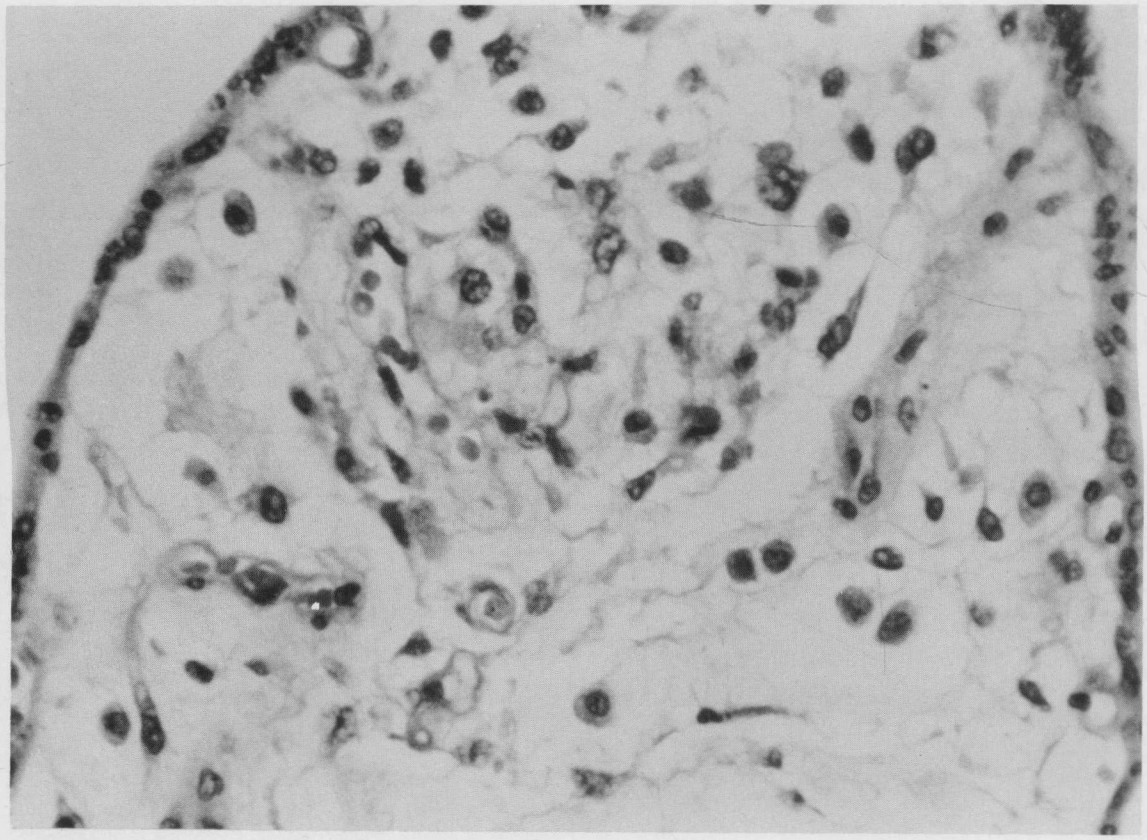

Figure 10
VILLOUS STROMA
Early third trimester, mildly hydroptic, vacuolated secondary villus with prominent stromal cells. Cells in the stroma with definable cytoplasm are Hofbauer cells, the apparently fixed reticuloendothelial elements. Note occasional syncytiovascular membrane formation at the edges of the villus. These vessels are paracapillaries (see page 7). X200.

Vascularization

In the protomesenchyme, some cells acquire a denser cytoplasm and appear to elongate, with two or three stellate projections. Several of these commonly appear in a given focus under the microscope and interconnect, surrounding a space or lumen (fig. 11). As these lacunae enlarge, other cellular elements appear in them, possibly arising from and differentiating away from the endothelial precursors. These are, in turn, the early vessels (blood lakes or blood islands) and the erythroblastic islands. As early as seven weeks, nucleated erythrocytes of surprisingly mature form are present in these lakes. Coalescence of the lakes leads to a true vascular system, in conjunc-

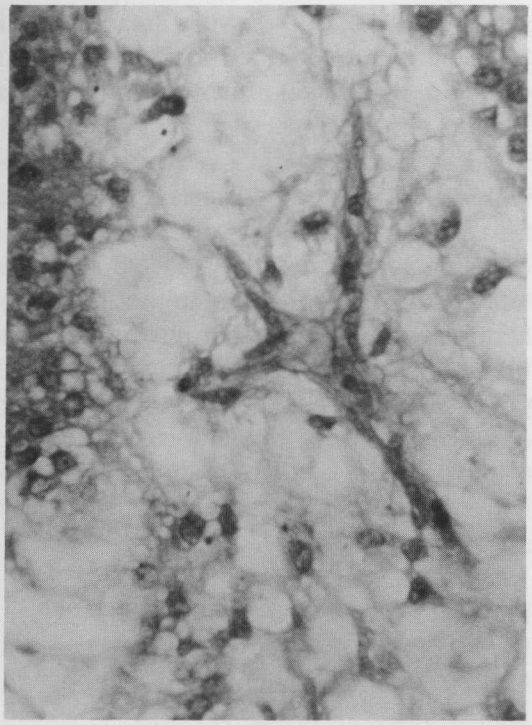

Figure 11
EARLY VILLOUS VASCULARIZATION
Stellate angiogenesis with partial lumen formation, in first trimester. Note vacuolated cytotrophoblast. X200.

tion with the developing fetal circulation. In the absence of this circulation, angiogenesis will arrest at an early stage and erythropoiesis will not go beyond a few stem cells. Ultimately there are two interconnecting vascular systems in the villi. These are the arterial-capillary-venous circuit and the paracapillary system of Bøe. This latter is a delicate network of small capillaries near the trophoblast of small villi and stems. There is no credible evidence for a lymphatic system.

The Reticuloendothelial System

The origin of the macrophagic cells of Hofbauer in the placenta is uncertain. Their origin de novo in the villous mesenchyme is suggested by the early stages at which they are seen, often before there is a fully competent fetal circulation to all parts of the placenta. On the other hand, they are more commonly seen in association with lacunae of hydroptic villi, but hydroptic villi with a circulation, as contrasted to the avascular hydrops seen in such conditions as chorionic molar pregnancy. As such, the metastatic formation of lymph nodes in the fetal body, described by Kyriazis and Esterly, may play some role in the populating of villi by specialized RE cells. This is one of many areas in which much more needs to be known for a fully functional understanding of the placenta.

The X Cell System

In the mature decidua, in both plate and septae, are polygonal, sharply defined cells with a single nucleus. The chromatin is vesicular. These are often isolated or clustered and commonly mingle with decidual cells from which they can easily be distinguished. The decidua is made up of large paler cells, often less well defined (fig. 12). The X cells often are found enmeshed in maternal fibrin within the decidual plate. They are usually without mitoses. Their function is unknown. Maidman and associates presented data to show fetal or trophoblastic origin. Similar cells sometimes seen next to trophoblastic "cysts" in the cell column are supportive of this view. Benirschke and Driscoll pointed out: (1) transitions from trophoblast are not seen; (2) they are not seen in trophoblastic tumors; and (3) their location is fairly constant at the interface. They consider these points as indicating a maternal origin. The corona radiata of the granulosa has