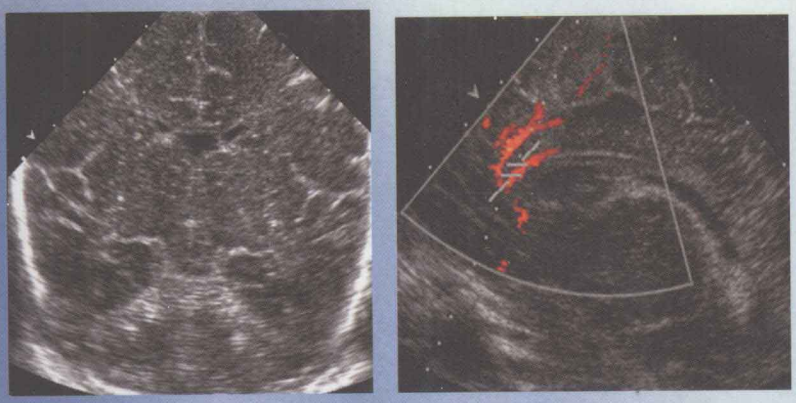
FETAL and NEONATAL BRAIN INJURY

FOURTH EDITION



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CAMBRIDGE
Medicine

Fetal and Neonatal Brain Injury

Fourth Edition

Edited by
David K. Stevenson
William E. Benitz
Philip Sunshine
Susan R. Hintz
Maurice L. Druzin

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Fetal and Neonatal Brain Injury

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Foreword

Neonatal–perinatal medicine emerged as a subspecialty in the 1960s, and the first certification examination by the American Board of Pediatrics took place in 1975. Prior to the application of intensive care, neonatal–perinatal medicine could be characterized as being anecdotally based, with benign neglect and a series of disastrous interventions. Great progress has been made, and evidence-based medicine is now the order of the day. The data base has expanded exponentially and we stand on the threshold of seminal therapeutic breakthroughs. The impossible is being made possible, and we anticipate that the ability to repair organs such as the brain and spinal cord will soon be part of our armamentarium.

There has been a dizzying proliferation of scientific knowledge related to the brain that has been incorporated into the fourth edition of *Fetal and Neonatal Brain Injury*. Whereas there is a general awareness that by the time a textbook is published it typically trails current knowledge, the editors have made every effort to remedy this. The fourth edition includes new authors or topic headings for 21 of the 50 chapters, and the text *is as near to current as is humanly possible.*

Simplifying neuroscience for non-neurologists is a daunting task. Yet somehow, through their choice of contributors, the editors have successfully assembled a book that is comprehensive, up to date, understandable, and interesting to read. The sections have been somewhat rearranged but they follow a logical sequence and new chapters and contributors blend seamlessly with those that have been updated. Although the text is mainly focused on the central and peripheral nervous system, because any and all disorders in the neonate may affect the brain, the reader is subjected to an excellent refresher course on general neonatology.

When I wrote the foreword to the third edition, we could anticipate the outcomes from the hypothermia for hypoxic ischemic encephalopathy trials – the data are available and encouraging. However, additional therapy is still needed as approximately half the treated group is still significantly harmed by the perinatal insult. Furthermore, there is a suggestion that the outcomes for extremely low-birthweight infants are improving. The developing brain is slowly revealing its secrets, and we can anticipate even better outcomes in the future.

The latest advances in genetics, neurobiology, and imaging as well as the therapeutic advances in the treatment of asphyxia and seizures, to mention a few, are well described. There are also a number of journeys that can be followed from bench to bedside. I came away with an optimistic feeling that we are on the brink of major breakthroughs in neuronal repair, as well as a deep respect for the plasticity of the brain. A Canadian psychiatrist, Norman Doidge, has called neural plasticity "one of the most extraordinary discoveries of the twentieth century." Neural plasticity permits the neonatal brain to move a given function to a different location as a consequence of normal experience or brain damage/recovery. Is it really possible that thinking, learning, and acting actually change the structure and function of the brain? Certainly there is every reason, based on the accumulating evidence, to believe this to be true. Better understanding of this remarkable ability will enable the maximum recovery from insults to the brain. Also the recognition and characterization of neuromodulators and neurotrophic factors, together with a better understanding of the genetic, hormonal, and cytokine control of the neurons, should result in the successful introduction of newer and better pharmacologic agents. Ultimately we can anticipate the implantation of cells genetically modified to secrete the appropriate cytokines, hormones, or therapeutic agents to modulate the brain.

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Preface

In preparing the fourth edition of our textbook, we have incorporated the newest data regarding the pathophysiology and cellular and molecular bases of neonatal encephalopathy. We have added the most recent data depicting the emergence of newer and promising forms of therapy, including the results of randomized clinical trials using hypothermia.

We have added two new editors for this edition, Dr. Maurice L. Druzin, who is the Chief of Maternal Fetal Medicine at Stanford University, and Susan R. Hintz, an Associate Professor of Pediatrics in the Division of Neonatal and Developmental Medicine. Dr. Druzin has reorganized the section on obstetrical factors that can contribute to fetal and neonatal brain injury and has recruited new contributors for this endeavor. Dr. Hintz, who has provided leadership in prenatal counseling and is the Director of our new Center for Comprehensive Fetal Health, has also focused on outcome studies in various disease processes in the neonate, and recruited new contributors to provide additional outcome data and recommendations.

We have added several new chapters, including ones addressing pregnancy-induced hypertension, HELLP syndrome and chronic hypertension, complications of multiple gestation, neurogenic disorders of the brain, pathogenesis of white-matter injury in the preterm infant, neonatal stroke, assessment and management of infants with cerebral palsy, the long-term outcome of neonatal events on speech, language development, and academic achievement, as well as the neurological outcome of infants with neonatal encephalopathy. We have expanded the chapters on the mechanism of brain damage in animal models of neonatal encephalopathy, the structural and functional imaging of the fetal and neonatal brain, and hemorrhagic lesion of the central nervous system.

As we noted in our previous editions, with any text that has multiple contributors, there is some overlap and repetition among the various presentations. Rather than editing these chapters to avoid such overlap entirely, we have elected to respect the authors' unique presentations and styles, as different perspectives reflect the richness of their experiences. It also allows the contributors to express their opinions freely, and the variation of opinion in similar topics can be appreciated more fully.

We thank our collaborators, especially those who met their editorial deadlines, as well as the staff of Cambridge University Press for their support and expertise in preparing the text. We thank Cele Quaintance, who helped organize the content of the text, maintained contact with our contributors, and collected and collated the chapters as they were received. We also thank Mrs. Tonya Gonzales-Clenney, who helped edit many of the chapters to fit the format of the text, and maintained communications with our publishers.

Lastly, we owe a great deal to our spouses, Joan Stevenson, Andrea Benitz, Sara Sunshine, Elizabeth Hoffman, and Henry Rosack, for their support, encouragement, and infinite patience.

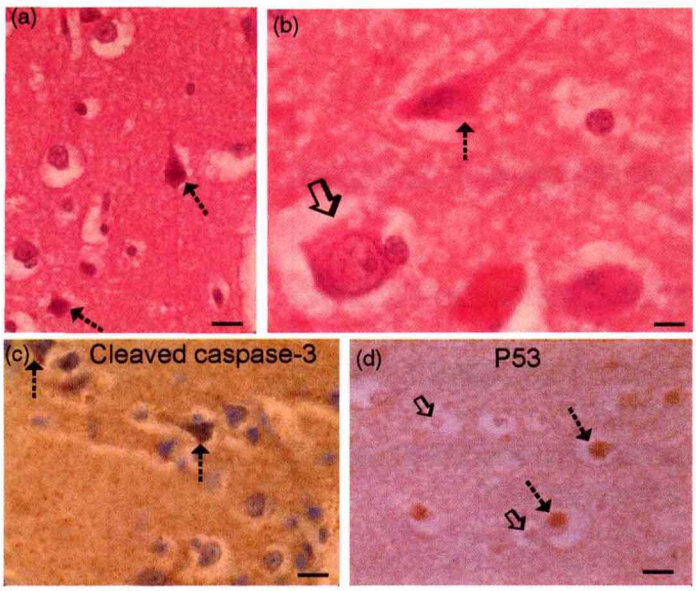


Fig. 2.6. Neuronal cell death in human newborn HIE. (a, b) Hematoxylin staining of neocortex from an infant that survived 3 days after HI due to delivery complications reveals selective degeneration of neurons (hatched arrows) in the form of typical ischemic neuronal death with eosinophilic cytoplasm, shrunken cell body, and condensed nucleus. Other damaged neurons are swollen with a vacuolated cytoplasm (open arrow in b). This pattern of neurodegeneration is much less phenotypically heterogeneous than that seen in neonatal rodent models of HI, but similar to that seen in our piglet model of HI. Scale bars = 33 μm (a), 7 μm (b). (c) Subsets of neocortical neurons (hatched arrows) in human infants with HIE display cleaved caspase-3 throughout the cell. Other cells in the field shown by the cresyl violet counterstaining have no labeling for cleaved caspase-3. Scale bar = 15 μm. (d) Subsets of neocortical neurons (hatched arrows) in human infants with HIE display active p53 within the nucleus. Other cells (open arrow) in the field have no labeling for active p53. Scale bar = 15 μm.

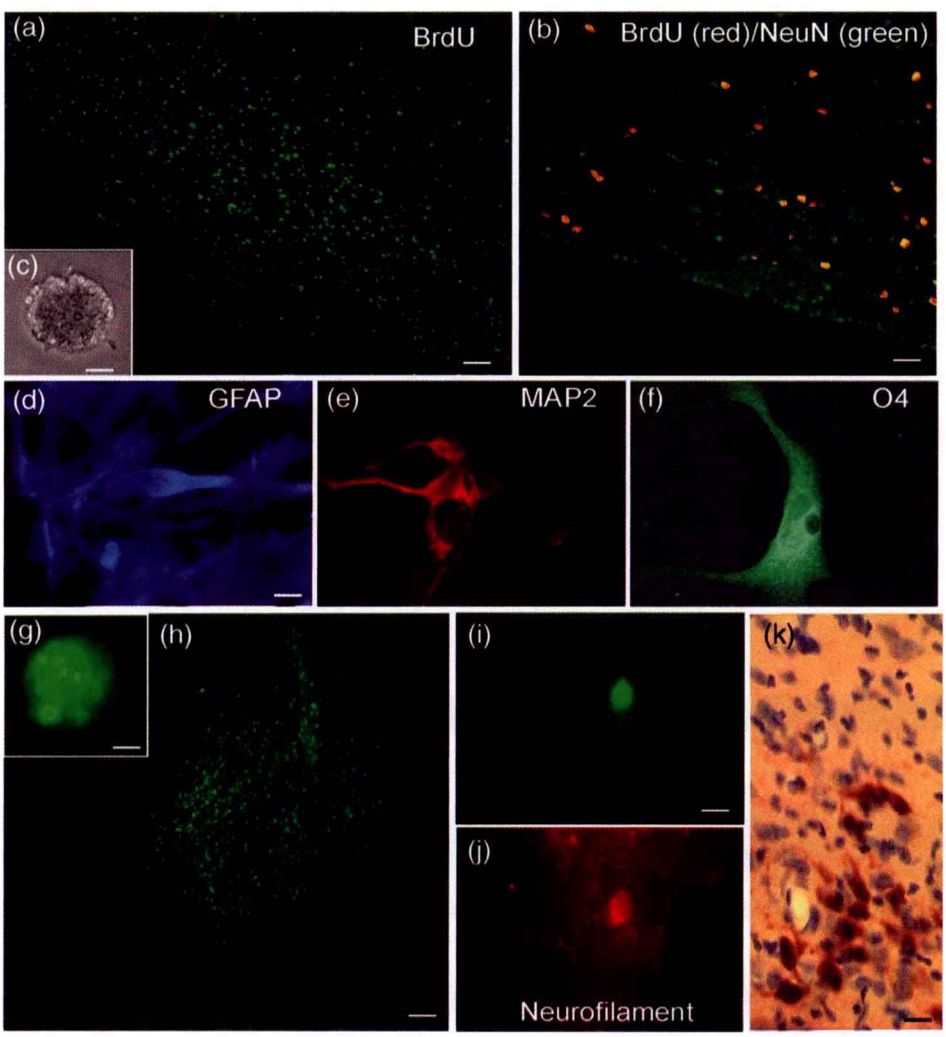


Fig. 2.7. The newborn piglet olfactory bulb (OB) is a rich source of multipotent neural progenitor cells useful for transplantation into damaged newborn brain after HI. (a) The piglet OB core (the ventricular cavity is the black area at left of image) contains numerous newly born cells (green-labeled cells) as identified by BrdU labeling of replicated DNA and antibody detection. Scale bar = 80 μm. (b) The majority of newly born cells (BrdU, red) in the newborn piglet OB core express the neuron-specific nuclear marker NeuN (green), demonstrating that they are newly born neurons. Yellow indicates overlap in two signals. Scale bar = 24 μm. (c) Newborn piglet OB-NSC/NPC neurosphere. OB core cells from newborn piglet can be harvested, cultured, and used to isolate neurosphere-forming cells. Neurospheres can be dissociated into constituent cells and shown by single-cell clonal analysis to be multipotent neural precursor cells. Scale bar = 20 μm. (d–f) Single OB core neurosphere-forming cells can be expanded in vitro to form numerous additional neurospheres with constituent cells that can differentiate into the three primary neural cell types: astrocytes positive for glial fibrillary (GFAP), neurons positive for microtubule-associated protein-2 (MAP2), and oligodendrocytes positive for the cell surface marker O4. Scale bar = 7 μm. (g) Piglet OB-NSC/NPC neurospheres can be stably transfected with a green fluorescent protein (GFP) gene using a lentiviral construct. This cell tagging serves as a reporter for transplanted cells. Scale bar = 20 μm. (h) After transplantation into the newborn piglet with HIE, GFP-OB-NSC/NPC neurospheres disperse entirely into individual green-labeled cells and migrate into damaged areas. Scale bar = 20 μm. (i, j) Subsets of transplanted GFP-labeled cells (green in i) in neocortex and basal ganglia that appear to be differentiating express neuron markers (neurofilament, red in j). Scale bar = 12 μm. (k) Immunoperoxidase detection of GFP using monoclonal antibody can be used as an alternative method to identify transplanted cells in HI piglet brain. These cells (brown-labeled cells) have engrafted, survived, and are differentiating into neurons in striatum. Scale bar = 20 μm.

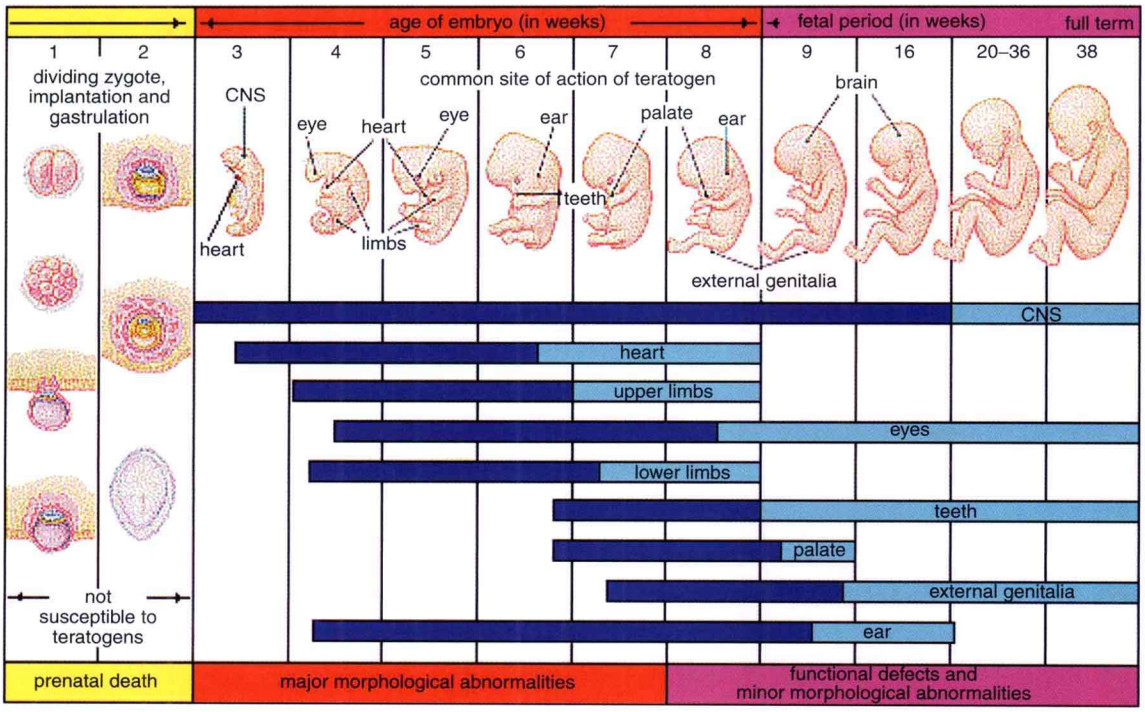


Fig. 10.1. Malformations by organ system as a function of gestational timing. Note that the embryo is not susceptible to teratogenic damage during days 0–10 post-conception. Adapted from: Moore KL, *Before We Were Born: Basic Embryology and Birth Defects*, 2nd edn. Philadelphia, PA: Saunders, 1993. With permission.

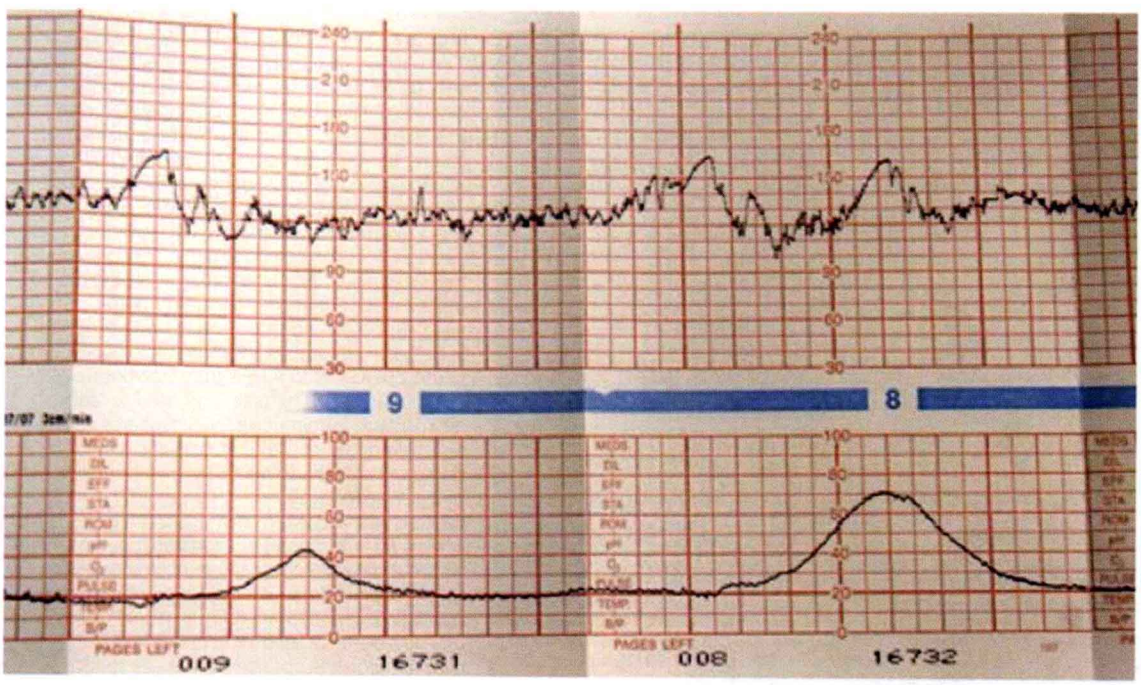


Fig. 15.1. Normal fetal heart-rate tracing. Within a 20-minute window a normal fetal heart-rate baseline is seen with normal (moderate) variability and two accelerations.

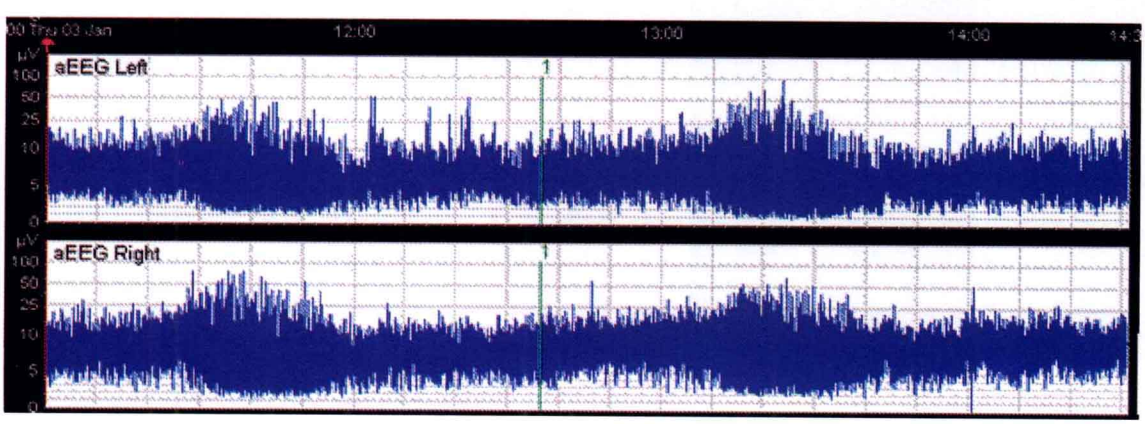


Fig. 17.8. Amplitude-integrated EEG in a healthy term infant. Example shows 3.5-hour recording. Broad portions of band correlate with quiet sleep; narrow portions correlate with active sleep.

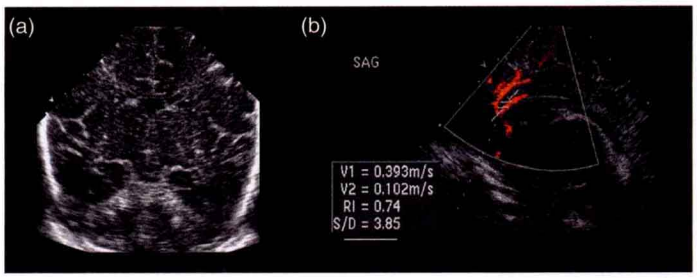


Fig. 18.1. Normal infant and child brain. Ultrasound (US) images of term neonate: (a) coronal US; (b) sagittal US + Doppler with resistive indices (RI).

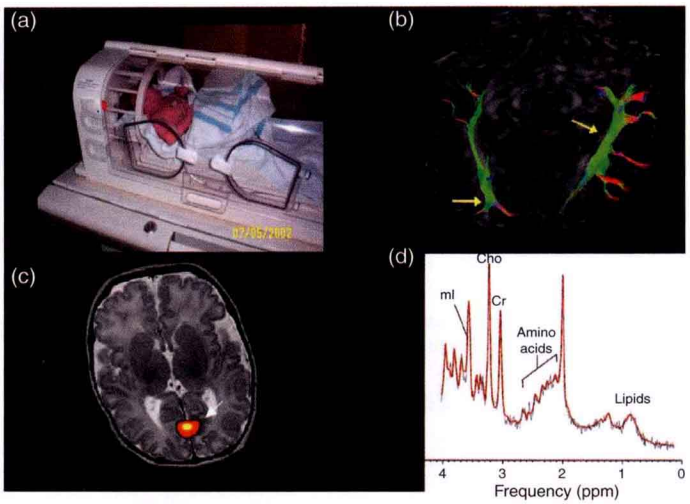


Fig. 18.2. (above) Advanced MRI techniques: (a) MR-compatible incubator; (b) DTI white-matter tractography (arrows); (c) fMRI (primary visual cortex activation: arrow); (d) MR spectroscopy (see text).

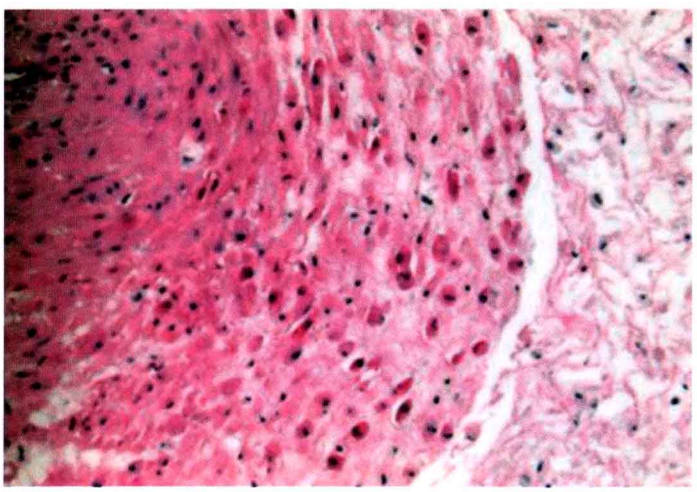
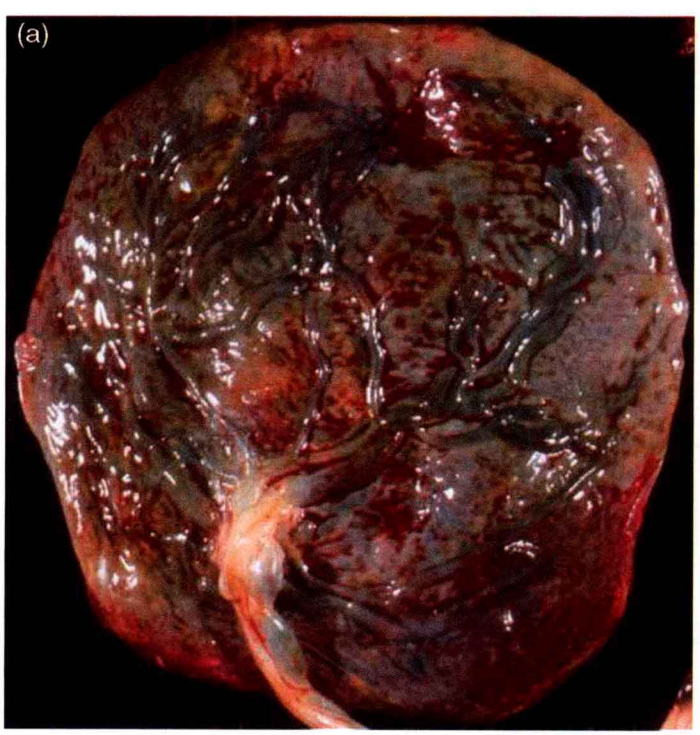


Fig. 20.1. (left) Meconium-induced umbilical vascular necrosis. Outer wall myocytes exhibit pyknosis in the presence of meconium macrophages.



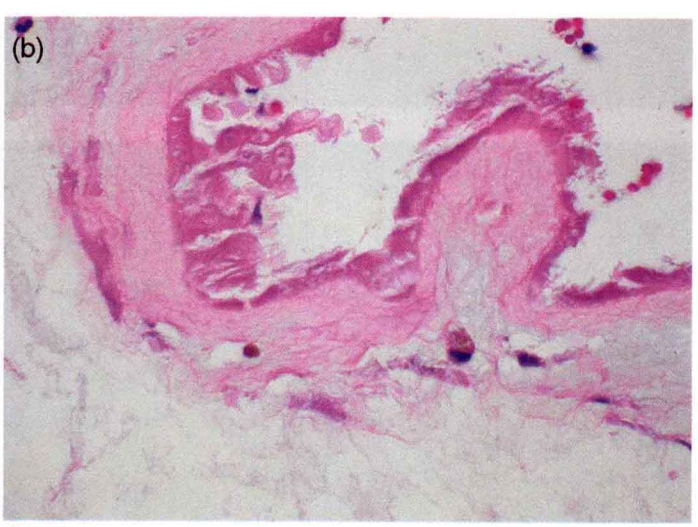


Fig. 20.2. (a) (left) Gross meconium staining: the fetal surface is discolored green to green-brown; the surface typically feels diffluent ("slimy") on palpation. (b) (above) Microscopic meconium uptake into membrane macrophages: through the microscope, meconium appears as a globular or amorphous orange-brown pigment; note the reactive amnion and amnion necrosis due to meconium.

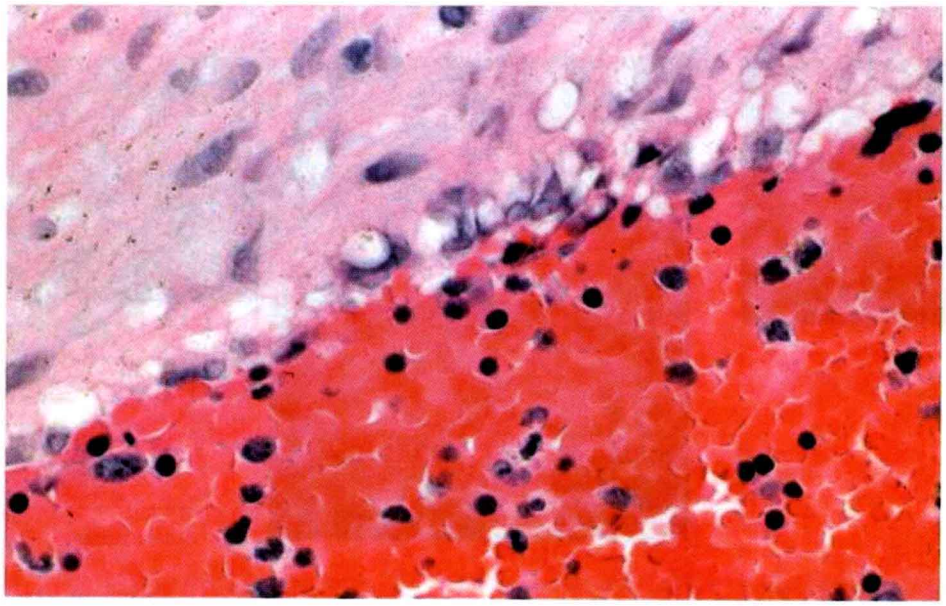


Fig. 20.3. Nucleated red blood cells (NRBCs) are identified by their round hyperchromatic nuclei and pink-red cytoplasm. NRBCs of this proportion indicate non-acute hypoxic stress, in this case from a stillbirth due to umbilical cord hypercoiling.

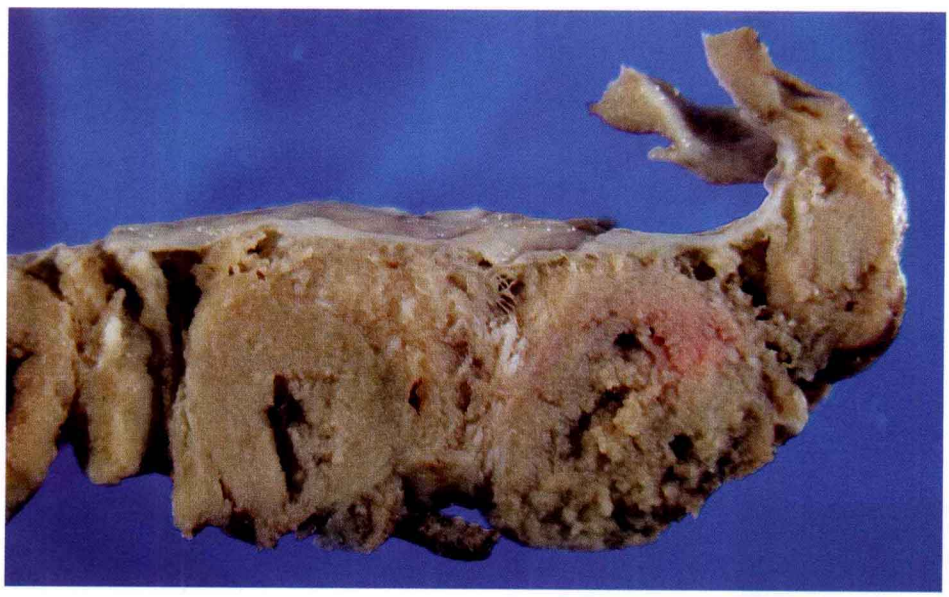


Fig. 20.4. Cut section of a formalin-fixed placenta from a severe fetomaternal hemorrhage. Note the markedly pale parenchymal tissue.

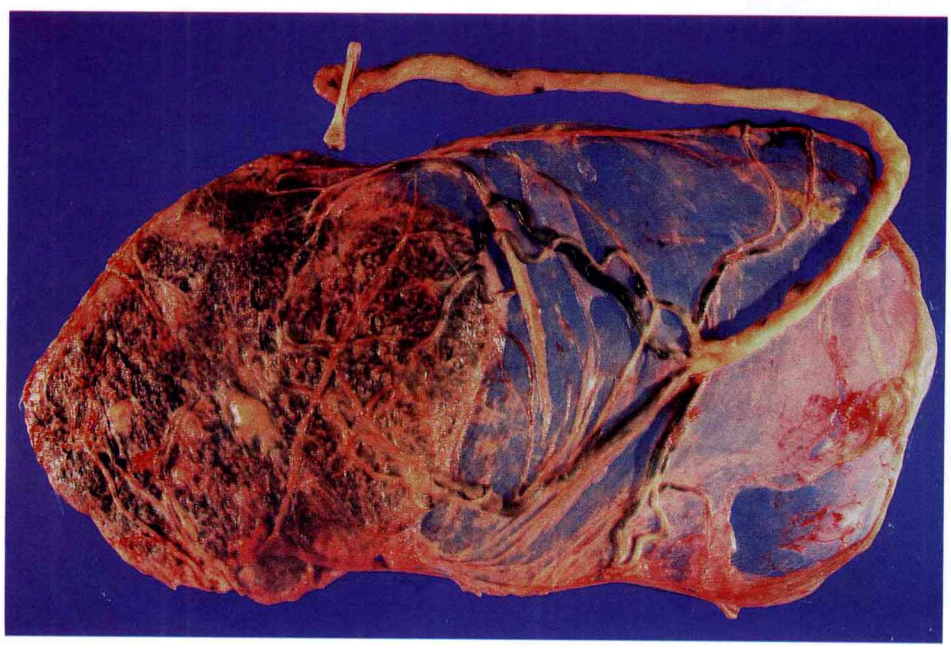


Fig. 20.7. Placenta with a velamentous insertion. Note that the umbilical cord inserts far from the placental margin and numerous membranous vessels are present. In this case, there is no disruption of vessels or hemorrhage in the surrounding membranes.

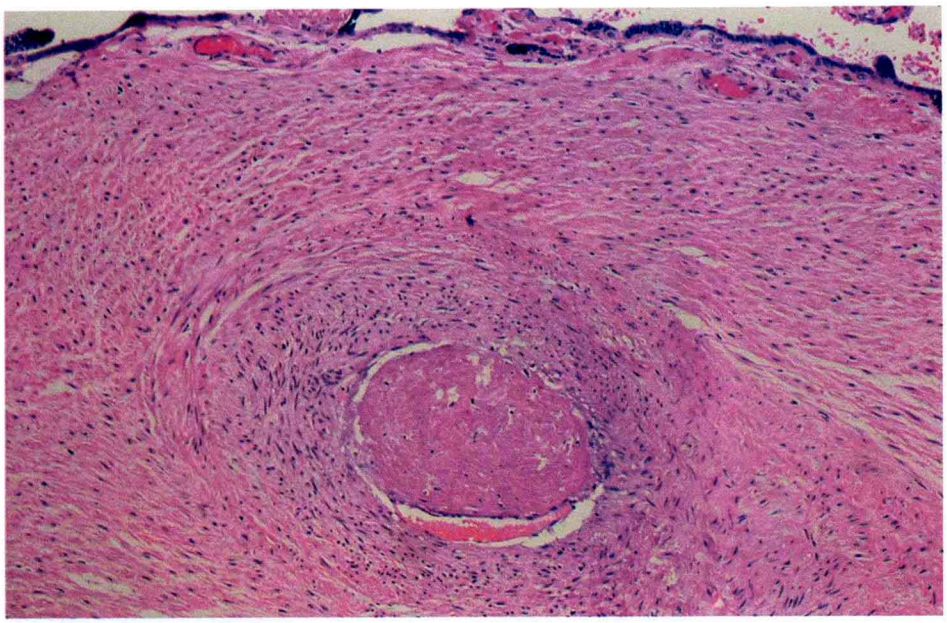


Fig. 20.8. Fetal vessel in a stem villus with a recent, nearly occlusive thrombus.

Fig. 20.9. Large fetal chorionic plate vessel with distension and partially occlusive thrombus. Calcification in the thrombus is indicative of chronicity.

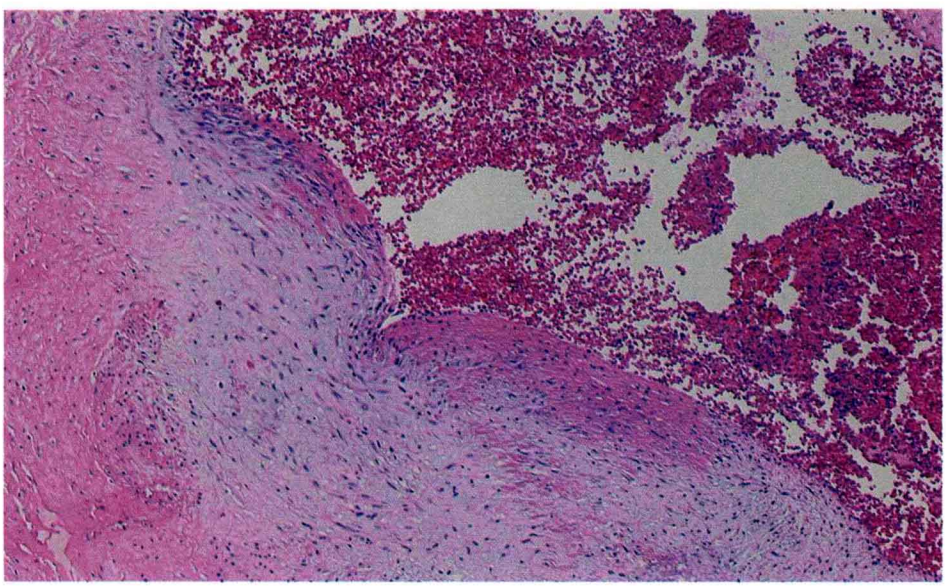


Fig. 20.10. Large fetal chorionic plate vessel with intimal fibrin cushion. Note fibrin deposition in the wall of the vessel in the lower left of the figure and deposition of pale-blue ground substance forming a "cushion."

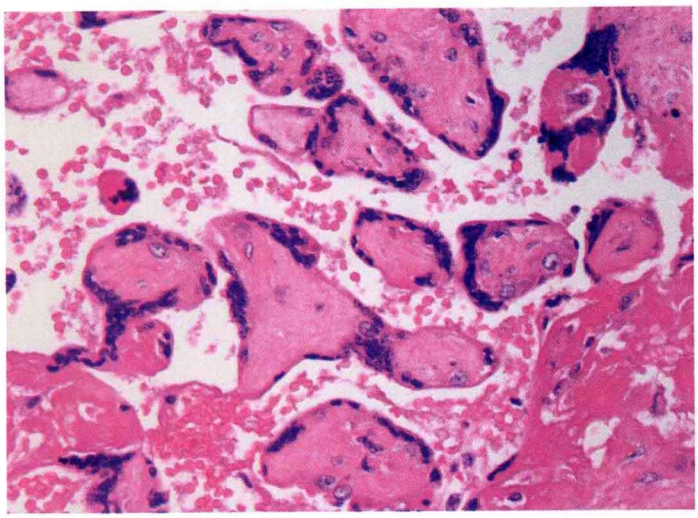


Fig. 20.11. Avascular villi. Focus of villi lacking any villous capillaries and with marked hyalinization of the stroma indicative of upstream fetal vascular thrombosis.

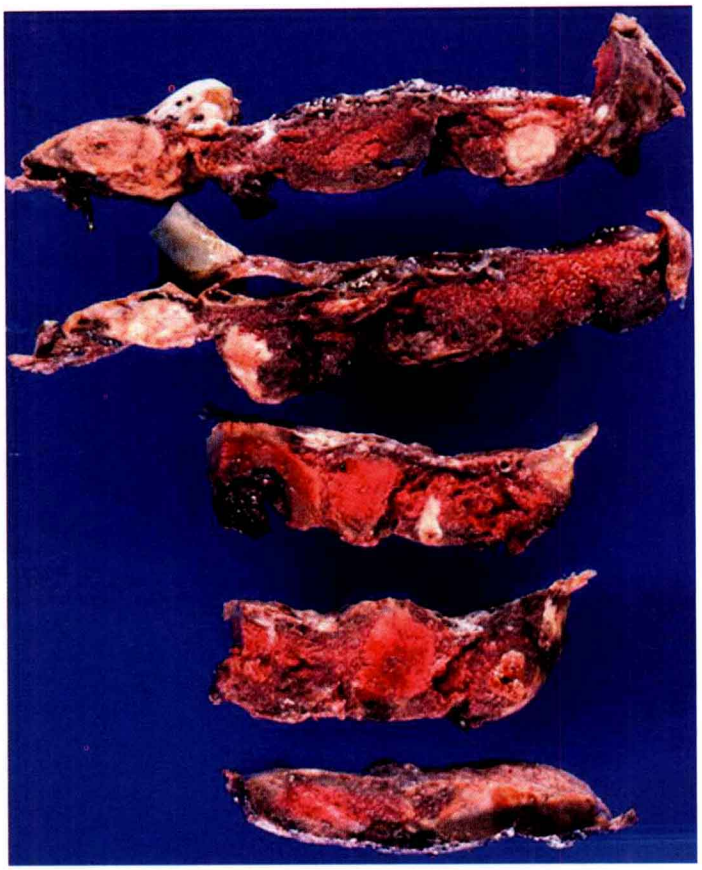


Fig. 20.13. (above) Gross pathology of intrinsic maternal vascular disease leading to chronic maternal vascular underperfusion. Multiple temporally heterogeneous infarcts, with or without placental abruption (present in this case, middle section on left).

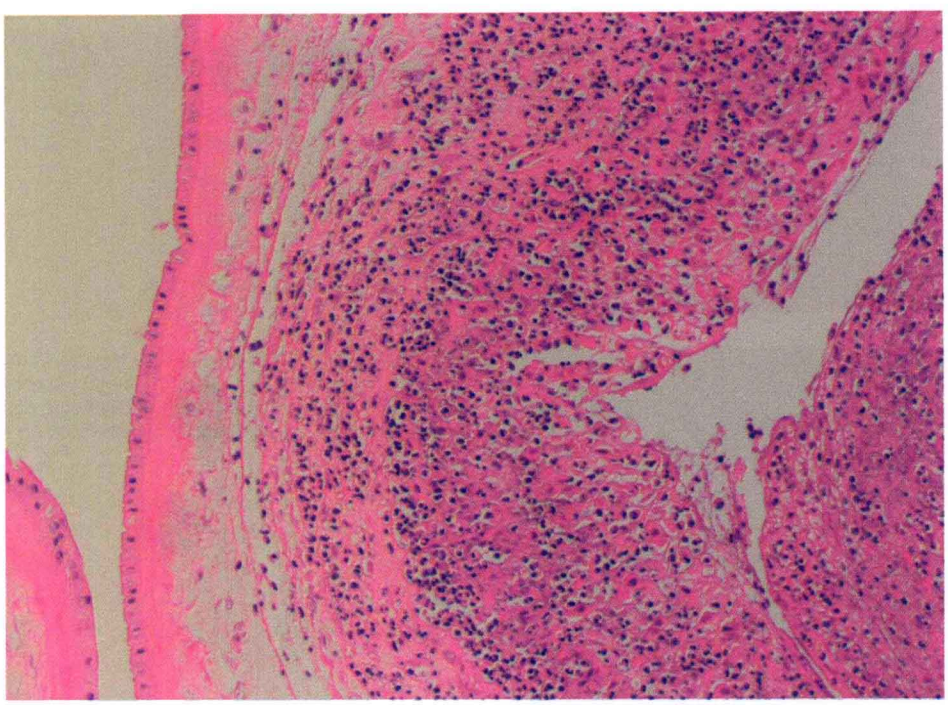


Fig. 20.12. Section of extraplacental membranes with acute chorioamnionitis. Notice infiltration of numerous neutrophils within all layers of the membranes: these are derived from the decidua and thus the maternal circulation.

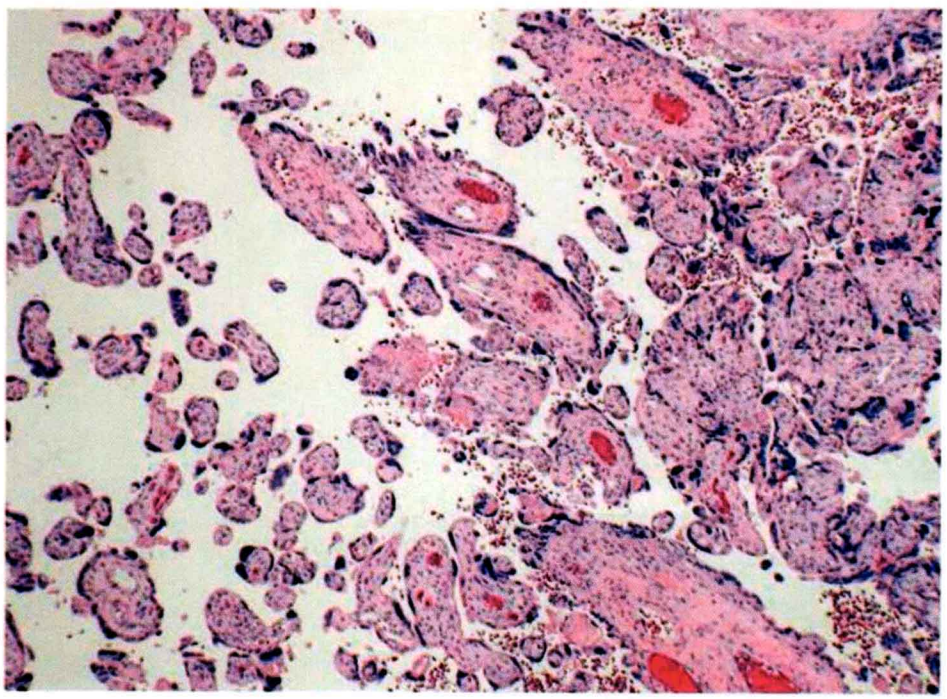


Fig. 20.14. Some of the microscopic features of chronic maternal underperfusion: villous ischemic changes, manifested as distal villous hypoplasia (on left) and villous agglutination (on right).

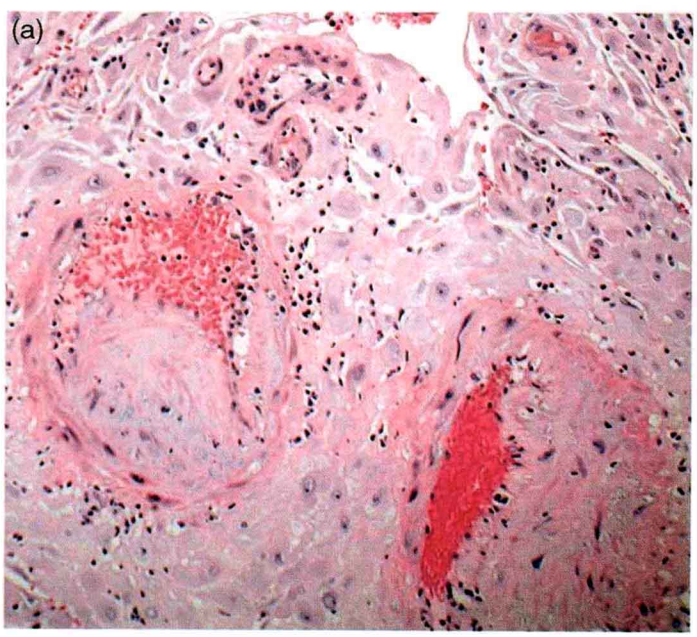


Fig. 20.15. (a) Decidual arteriopathy. Milder phenotype: non-transformation of spiral arterioles.

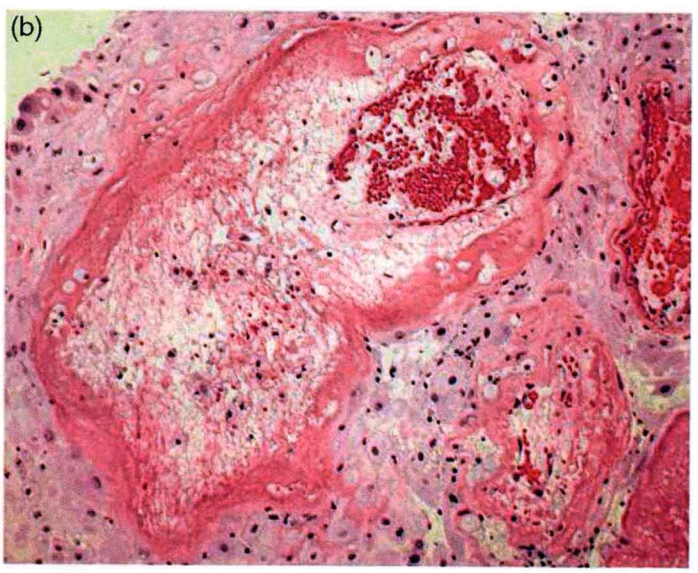


Fig. 20.15. (b) Decidual arteriopathy. More severe phenotype: fibrinoid necrosis with acute atherosis.

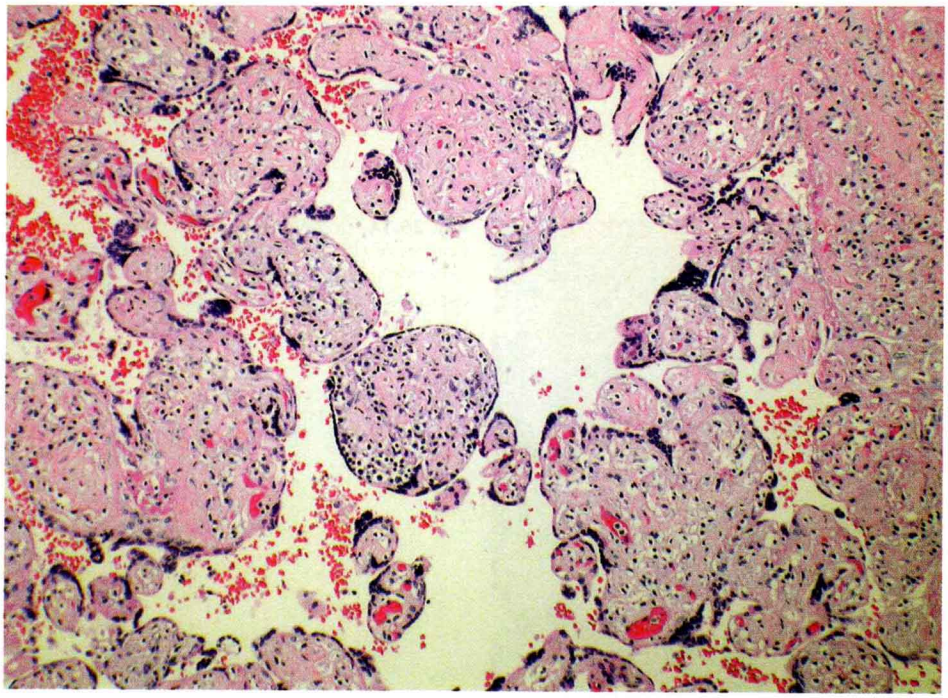


Fig. 20.16. Severe chronic villitis. Widespread obliteration of terminal villous capillaries and distal stem villous vessels (so-called obliterative vasculopathy).

Fig. 20.17. (a) Massive perivillous fibrin deposition (MPFD). Grossly, affected regions appear dense and off-white.

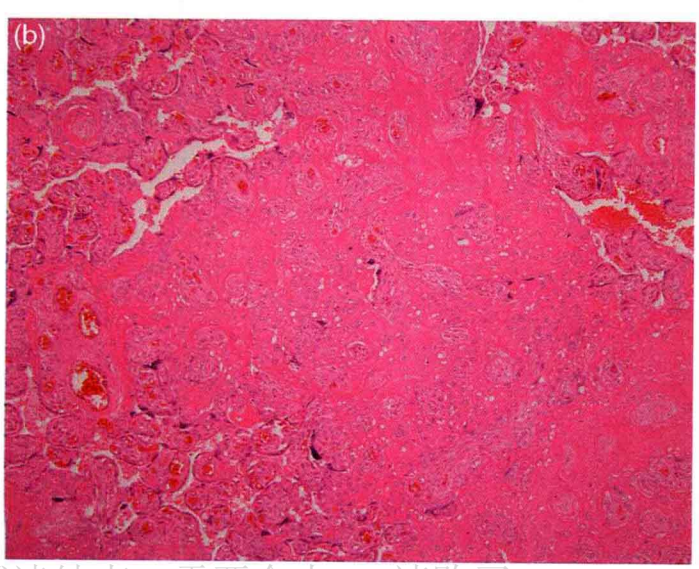


Fig. 20.17. (b) Massive perivillous fibrin deposition (MPFD). Microscopically, affected regions demonstrate intervillous deposition of pink (eosinophilic) material, so-called fibrin(oid).