

Contents

Preface	xiii
Adré J. du Plessis	
The Molecular and Genetic Mechanisms of Neocortex Development	503
Alejandro L. Diaz and Joseph G. Gleeson	
<p>This article reviews key recent findings in the field of human cortical development. This development is divided into three major time-dependent phases: neural proliferation of inhibitory and excitatory neurons in spatially distinct regions, migration through multiple cellular boundaries, and maturation through morphologic changes that result in the elaboration of dendrites and axons and that establish the multitude of cellular contacts that underlie neuronal processing. Many of the neurocognitive disorders treated in the clinic can trace their origin to a disorder in one or more of these key steps. Along with this update, work is highlighted that offers a glimpse at the future of therapy for developmental brain disorders that can result from disorders of these cellular events.</p>	
Development of the Human Cerebellum and Its Disorders	513
Hans J. ten Donkelaar and Martin Lammens	
<p>The cerebellum arises from two anatomically and molecularly different proliferative compartments: the cerebellar ventricular zone and the rhombic lip. The protracted development makes the cerebellum vulnerable to a broad spectrum of developmental disorders, of which the more frequent (the Dandy-Walker and related malformations and the pontocerebellar hypoplasias) are discussed in this article. Several genes for congenital malformations of the human cerebellum have recently been identified, including genes causing Joubert syndrome, the Dandy-Walker malformation, and pontocerebellar hypoplasias.</p>	
Cerebral Blood Flow and Metabolism in the Developing Fetus	531
Adré J. du Plessis	
<p>The inaccessibility of the human fetal brain to studies of perfusion and metabolism has impeded progress in the understanding of the normal and abnormal systems of oxygen substrate supply and demand. Consequently, current understanding is based on studies in fetal animals or in the premature infant (ex utero fetus), neither of which is ideal. Despite promising developments in fetal magnetic resonance imaging (MRI) and Doppler ultrasound, major advances in fetal neurodiagnostics will be required before rational and truly informed brainoriented care of the fetus becomes feasible.</p>	

Disorders of Placental Circulation and the Fetal Brain

549

Raymond W. Redline

Disorders of the placental circulation, including the release of deleterious mediators to the fetus, are important risk factors for central nervous system complications. These disorders result in discrete patterns of placental injury detectable by a thorough placental pathologic examination. Consideration of the location, severity, multiplicity, and timing of these lesions is critical to a full understanding of their significance. Less than 10% of placentas from term infants that later develop cerebral palsy lack any evidence of placental abnormalities potentially related to adverse outcome.

Disorders of the Fetal Circulation and the Fetal Brain

561

Catherine Limperopoulos

Even in the presence of normal placental function, cerebral oxygen-substrate supply may be disrupted by disturbances in the fetal circulation caused by anomalous cardiac development. The impact of these cardiac lesions is likely dictated primarily by the volume and oxygen-substrate composition of transverse aortic arch perfusion. Advances in fetal echocardiography, fetal Doppler ultrasound, and advanced fetal magnetic resonance imaging techniques capable of quantitative structural and functional measurements are providing major insights into the *in vivo* effects of these cardiac lesions on brain growth and development. The progress to date with the application of these techniques is reviewed in this article.

Fetal Hypoxia Insults and Patterns of Brain Injury: Insights from Animal Models

579

Alistair Jan Gunn and Laura Bennet

The outcome of perinatal hypoxiaischemia is highly variable, with only a very broad relationship to the 'severity' of oxygen debt as shown by peripheral base deficit and the risk of damage. The present article examines the pathophysiology of asphyxial injury. We dissect the multiple factors that modify the risk of injury, including the depth ('severity'), duration, and repetition of the insult, the maturity, and condition of the fetus, pre-existing hypoxia, and exposure to pyrexia and infection/inflammation.

Fetal Effects of Psychoactive Drugs

595

Amy L. Salisbury, Kathryn L. Ponder, James F. Padbury, and Barry M. Lester

Psychoactive drug use by pregnant women has the potential to effect fetal development; the effects are often thought to be drug-specific and gestational age dependent. This article describes the effects of three drugs with similar molecular targets that involve monoaminergic transmitter systems: cocaine, methamphetamine, and selective serotonin re-uptake inhibitors (SSRIs) used to treat maternal depression during pregnancy. We propose

a possible common epigenetic mechanism for their potential effects on the developing child. We suggest that exposure to these substances acts as a stressor that affects fetal programming, disrupts fetal placental monoamine transporter expression and alters neuroendocrine and neurotransmitter system development. We also discuss neurobehavioral techniques that may be useful in the early detection of the effects of in utero drug exposure.

Primary Disorders of Metabolism and Disturbed Fetal Brain Development 621

Asuri N. Prasad, Gustavo Malinger, and Tally Lerman-Sagie

There exists a link between the in utero metabolic environment and the development of the fetal nervous system. Prenatal neurosonography offers a unique, noninvasive tool in the detection of developmental brain malformations and the ability to monitor changes over time. This article explores the association of malformations of cerebral development reported in association with inborn errors of metabolism, and speculates on potential mechanisms by which such malformations arise. The detection of cerebral malformations prenatally should lead to a search for both genetic etiologies and inborn errors of metabolism in the fetus. Improving the changes of an early diagnosis provides for timely therapeutic interventions and it is hoped a brighter future for affected children and their families.

Fetal Infections and Brain Development 639

James F. Bale Jr

Current microbial diagnostics enable rapid and specific identification of the agents causing intrauterine and perinatal infections, and CT and MRI allow precise characterization of the central nervous system effects of these pathogens. Although infections with *Toxoplasma gondii*, *Toxoplasma pallidum*, *Toxoplasma cruzi*, and cytomegalovirus cannot currently be prevented by immunization, postnatal therapy of infected neonates can substantially improve outcome. Therapy with acyclovir should be initiated whenever perinatal herpes simplex virus encephalitis is suspected. Despite these strategies, intrauterine and perinatal infections remain major causes of permanent deafness, vision loss, cerebral palsy, and epilepsy among children throughout the world.

The Fetal Heart Rate Response to Hypoxia: Insights from Animal Models 655

Laura Bennet and Alistair Jan Gunn

This article examines recent studies that have systematically dissected features of fetal heart rate responses to labor that may help identify developing fetal compromise, such as the slope of the deceleration, overshoot, and variability. Although repeated deep decelerations are never necessarily benign, fetuses with normal placental reserve can fully compensate even for frequent deep but brief decelerations for surprisingly prolonged intervals before developing profound acidosis and hypotension.

Probing the Fetal Cardiac Signal for Antecedents of Brain Injury**673**

Adam J. Wolfberg and Errol R. Norwitz

Obstetric care providers and researchers have long relied on analysis of the fetal heart rate tracing for insight into the fetal neurologic status. Although a normal fetal heart rate tracing does provide reassurance of intact neurologic function, an abnormal pattern is a very poor predictor of newborn brain injury. Indeed, if the clinical end point of interest is cerebral palsy, a non-reassuring fetal heart rate tracing has a 99% false positive rate. More recent analyses of fetal heart rate variability and fetal ECG waveforms, however, hold promise for improved diagnostic accuracy.

The Current State and Future of Fetal Imaging**685**

Romy Chung, Gregor Kasprian, Peter C. Brugger, and Daniela Prayer

Fetal magnetic resonance imaging (MRI) may add important diagnostic information to prenatal sonography and has the power to confirm or change decisions at critical points in clinical care. Recent studies have shown MRI to be a critical clinical adjunct in the evaluation of the developing central nervous system (CNS), especially at early gestational ages, and MRI has been used in three significant ways: (1) for the quantification of brain growth and structural abnormalities using biometry, (2) for the qualitative evaluation of CNS microstructure, and (3) for the qualitative assessment of dynamic fetal movements in utero.

Fetal Neurological Assessment Using Noninvasive Magnetoencephalography**701**

Curtis L. Lowery, Rathinaswamy B. Govindan, Hubert Preissl, Pam Murphy, and Hari Eswaran

SQUID Array for Reproductive Assessment is a unique magnetoencephalography device designed for the noninvasive recording of fetal brain activity. In this article, we provide a general overview of the technology and its potential application to fetal medicine. A large number of studies that have been conducted and published describing this device since it was brought into operation are referenced throughout the article.

Index**711**