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Handbook of Pediatric Autopsy Pathology

Second Edition

Foreword by
John M. Opitz

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Dr. John Opitz and Dr. Lewis Barness
My two heros!

—Enid Gilbert-Barness

To my husband, Gary Myers; my parents, Agnes and Bjorn Steffensen;
and in memory of my father-in-law, Dr. Ivan Myers.

—Thora S. Steffensen

To my husband, Scott, and son, Andrew, for all of their support
and to my parents, Charles and Patricia Debich.

—Diane E. Spicer

Foreword

All workers in pediatric and fetal pathology must acknowledge with deep gratitude the massive effort required to revise this book, first published in 2005. It immediately became the standard text for daily use; no autopsy protocol goes out from our service without citation of the Handbook; at times it seems that the residents and fellows must know most of it by heart. It is so far more than a dry recital of facts and data and useful in so many ways concerning growth, development, and developmental pathology, expertly written and beautifully illustrated.

Since 2005, a veritable revolution has occurred in our specialty. Huge advances in developmental biology in many species make it now extensively possible to infer pathogenesis, if not cause, from phenotype and known animal "models" involving defined signal transduction pathways. This work has also enabled a profound insight into the relationship between evolution and development and, not incidentally, an appreciation of Meckel's prescient understanding (1812) that primary malformations are not contrary to nature, particularly if they represent the normal anatomical state in other species—think: absent corpus callosum, cleft palate, penoscrotal inversion, tail, cloaca, webbed digits, polymastia, etc. Thus, there is great usefulness after all in the concept of atavisms (Darwin's reversions), Ruppert A Willis (1958) notwithstanding. In a nutshell: Everything that develops, whether normal or abnormal, has evolved. And the antiquity of these morphogenetic mechanisms is truly astonishing, even more so the fact that many of these mechanisms are present, in potentiam, in organisms without the corresponding organ or body part—think only of Amphioxus with all the genes for it but no neural crest. As more and more basal organisms are "sequenced," this will become a common insight.

As important are the recent technical advances such as microarray analyses which allow detection of additional causal deletions and/or duplications not detectable by standard karyotype analysis. Or the gas chromatography/mass spectrometry methods do detect previously biochemically intractable abnormalities of sterol metabolism that may result in fetal/infant death. And not least, the newer radiological methods which improve detection e.g. of cervical ribs as a "litmus test" for lethal developmental disorders such as aneuploidy or childhood cancer.

Thus, the completion of this revision of the Gilbert-Barness and Debich-Spicer Handbook with the addition of Dr. Thora Steffensen comes at an extraordinarily propitious time in the history of pathology promising to help us advance even more rapidly our understanding of developmental pathology.

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Foreword from the 1st Edition

It is a profoundly gratifying and joyous occasion to welcome and recommend Gilbert-Barness and Debich-Spicer's *Handbook of Pediatric Autopsy Pathology*, the distillation of a professional lifetime of experience, practice, and discovery by one of the world's most distinguished pediatric pathologists (ably assisted by her coworker D. Debich-Spicer).

For over a third of a century I have been privileged to collaborate closely, at first as fellow faculty member in Madison, subsequently in a long-distance consultative relationship (Helena to Madison, and finally Salt Lake City to Tampa) with one of the most tireless and devoted experts in constitutional, pediatric, developmental, and genetic pathology. Initially it was for me, as apprentice, to learn from this peerless teacher, the practical aspects of studying dead fetuses and infants for inferences of pathogenesis and cause, with the aim to attain diagnosis and a deeper understanding of the underlying biology of the condition.

This was an apprenticeship which arose, long ago, out of a combined NIH Medical Genetics Research Center Grant at the University of Wisconsin in which we studied together, whenever possible, the infants and children before death, and after death with all of our trainees, involving coworkers in anatomy, genetics, embryology, and pathology.

An apprenticeship moreover that motivated me to continue the vitally (meant literally) important study of dead embryos, fetuses, and infants in Montana, part of a region (including Idaho, Montana, Wyoming, North and South Dakota, and Nevada) without a single pediatric pathologist. This regional fetal genetic pathology program could not have functioned without the almost daily advice and input of Dr. Gilbert-Barness and her coworkers.

In recognition of her role as one of the most highly regarded pathology teachers in the world, the University of Wisconsin created the distinguished Enid Gilbert-Barness Lectureship before her departure to the University of South Florida. She has been President of the Society of Pediatric Pathology, the International Pediatric Pathology Association and of several related organizations, has taught on every continent (except Antarctica), was a founder of the International Workshops of Fetal Genetic Pathology, is the editor of the two volume *Potter's Pathology of the Fetus and Infant* (under revision) with its companion Atlas, and the author (with D. Debich-Spicer) of *Embryo and Fetal Pathology* (2004), and with her husband, Lewis A. Barness, author of *Metabolic Diseases: Foundations of Clinical Management, Genetics, and Pathology*, vol. 2 (2000), and *Clinical Use of Pediatric Diagnostic Tests* (2003).

Recently, Dr. Gilbert-Barness (with a group of enthusiastic editorial coworkers) undertook the editorship of the journal *Fetal and Pediatric Pathology*, a journal which recognizes the important contributions to the study and biology of fetal and pediatric death by many other specialists, including embryologists, developmental biologists, and geneticists, experts in maternal-fetal medicine, metabolic diseases, peri- and neonatology, and clinical geneticists.

The present book is an intensely practical, profusely illustrated, and most useful treatise, published at a propitious time in history, e.g., the formation of the International College of Fetal Genetic Pathology and the initiation of the NICHHD-sponsored and NICHHD-supported multicenter study of the causes of stillbirth for both of which this book can serve as a guide for minimal standards in the practice of the causal analysis of fetal and infant death. In reading this book, I had the vivid experience of having revisited the grove of Akademe with my mentor in recognizing so many of the patients Dr. Gilbert-Barness and I have studied together.

Medicine arose out of the study of pathology, one of the most important foundations of biomedicine. And western pathology arose out of observations of malformations preserved in folklore and the notes of early surgeons (e.g., Pare, John Hunter) and physician/naturalists (e.g., Aldrovandi), but was not established as a legitimate medical specialty per se until Giovanni Battista Morgagni (1682–1771), a student of Valsalva and Professor of Pathological Anatomy at Padova for 56 years. His three-volume treatise *De sedibus et causis morborum per anatomen indagatis* (1779) is no less erudite than the present book, but in over 1,500 pages has not a single illustration in it. François Xavier Bichat (1771–1802), a gifted observer, founded histological pathology through his careful study of tissues or "membranes" in disease. Matthew Baillie (1761–1823), nephew of John Hunter and physician of George III, published his wonderful *Morbid Anatomy* with many excellent engravings, that of pulmonary emphysema illustrating the lungs of Dr. Samuel Johnson. Carl (von) Rokitansky (1804–1878), a Czech, was Professor of Pathology at Vienna for 30 years, and, like our present authors, performed thousands of autopsies, and from this experience published a much-admired, clear, multivolume compendium on pathology that remained the standard for decades. Of his four sons, he said that the two who were physicians healed (heilen), the two who were musicians howled (heulen). Rudolf (von) Virchow (1821–1902) initially Professor of Pathology in Würzburg, then in Berlin, was the founder of Cellular Pathology, founder and for decades editor of the *Archiv für pathologische Anatomie* ("Virchows Archiv…"), who is additionally renowned as an anthropologist and an advocate for democracy and social justice with the courage to stand up against Bismarck in Parliament.

Subsequent developments in infections, genetics, and molecular biology have transformed the face of pathology, but never the guiding sentiment of this book: *Mantui vivas docueran*: Let the dead teach the living. *Handbook of Pediatric Autopsy Pathology* stands as a worthy successor to those of the immortal giants mentioned above, who began, while they continue, to enrich our knowledge of life and death and have set highest standards for its study. This is one of those dozen or so books on the first shelf right over my head at my desk where I can reach it at all times without looking, altogether indispensible for the study and practice of developmental pathology.

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Preface

The first edition of this text was published in 2005, and at that time was written with the explicit aim to fill a void in pediatric autopsy pathology. The autopsy still remains of paramount importance for accurate diagnoses, genetic counseling, and for the definitive diagnosis in many malformations and complex genetic conditions and, in particular, in fetal and perinatal pathology.

Pediatric pathology includes examination of the embryo, fetus, and child. Of particular importance is the study of the aborted embryo that is so frequently totally neglected. We have, therefore, included specifically a chapter on the examination of the embryo.

In this volume, we have attempted to expand on the application of molecular and special recently described procedures such as DNA determination, enzyme analysis, and microarrays. The general format of the book has been maintained, but each chapter has been revised and expanded. In addition, black and white pictures have been replaced by color illustrations, and many new pictures and tables have been added. The additions of several chapters include skin, infectious diseases, hematopoietic diseases, tumors of childhood, and transplantation rejection.

We are pleased to have been able to add Dr. Thora S. Steffensen as an additional author.

It is our hope that this second edition will provide meaningful information and will assist in making the pediatric autopsy not only of paramount importance but an essential part of understanding the manner and cause of death in its broadest and comprehensive sense.

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Preface from the 1st Edition

The *Handbook of Pediatric Autopsy Pathology* has been compiled to fill a current void in the armamentarium for the pathologist performing the pediatric autopsy. The pediatric autopsy must be approached with great care in technique and dissection; malformations may be easily overlooked by the uninitiated. Of major importance in pediatric autopsy pathology is the need for accurate diagnosis in order to provide genetic counseling and the implication of possible recurrence in future pregnancies.

Although adult autopsies have declined in recent years, the importance and demand for pediatric autopsies has accelerated. There have been extensive developments in the pediatric field that enhance the importance of the autopsy, so that at the present time, the autopsy has probably greater importance within the field of the fetal and perinatal pathologist than at any other age. These features largely relate to congenital malformations and genetic counseling. The detailed description of all abnormalities in both fetuses, stillborn, and older children is of paramount importance supplemented by cytogenetic studies, metabolic evaluation, and DNA and other analyses.

The effect of any environmental or nutritional hazard is most obvious when related to periods of growth, and the fetus and the newborn are such periods in human development. Thus, any new environmental hazard and the effects of environmental agents and drugs including chemicals such as lead or radioactive materials, alcohol, or intrauterine infection, can and are best assessed by sampling specific tissues and organs from fetuses, stillborns, and newborn infants at autopsy examination.

The careful performance of perinatal autopsies followed by dissemination of the findings to parents, clinicians, and public health organizations is important in the reduction of perinatal mortality and morbidity. Every pathologist should have a working knowledge of the pediatric autopsy.

The careful performance of neonatal autopsies both adds to our basic understanding of neonatal diseases and is an excellent monitor of the results of treatment.

The development of perinatology, prenatal diagnosis of birth defects, and genetic counseling requires accuracy of prenatal diagnostic techniques, including ultrasonography and correlation of clinical data with the results of carefully performed fetal autopsies. Parents and clinicians depend on accurate autopsy diagnoses for intelligent family planning.

The autopsy examination is the foundation upon which a complete perinatal autopsy is built. In addition to the performance of a skilled autopsy biopsy, other ancillary studies and techniques are necessary to address the vital issues of accurate diagnosis. The *Handbook of Pediatric Autopsy Pathology* thoroughly addresses these issues including microbiologic, cytogenic, X-ray, and special studies such as enzyme and DNA analysis in metabolic diseases. This handbook also addresses the examination of the embryo in spontaneous abortions. The approach outlined is simple enough to be used routinely by the general pathologist with conventional facilities.

Parts I and II provide principles and a general description of the techniques used in the pediatric autopsy as well as general aspects of the autopsy including the death certificate, cause and manner of death, obtaining permissions from the family, and examination of the placenta. Part III includes hydrops, chromosomal defects, and congenital abnormalities, with