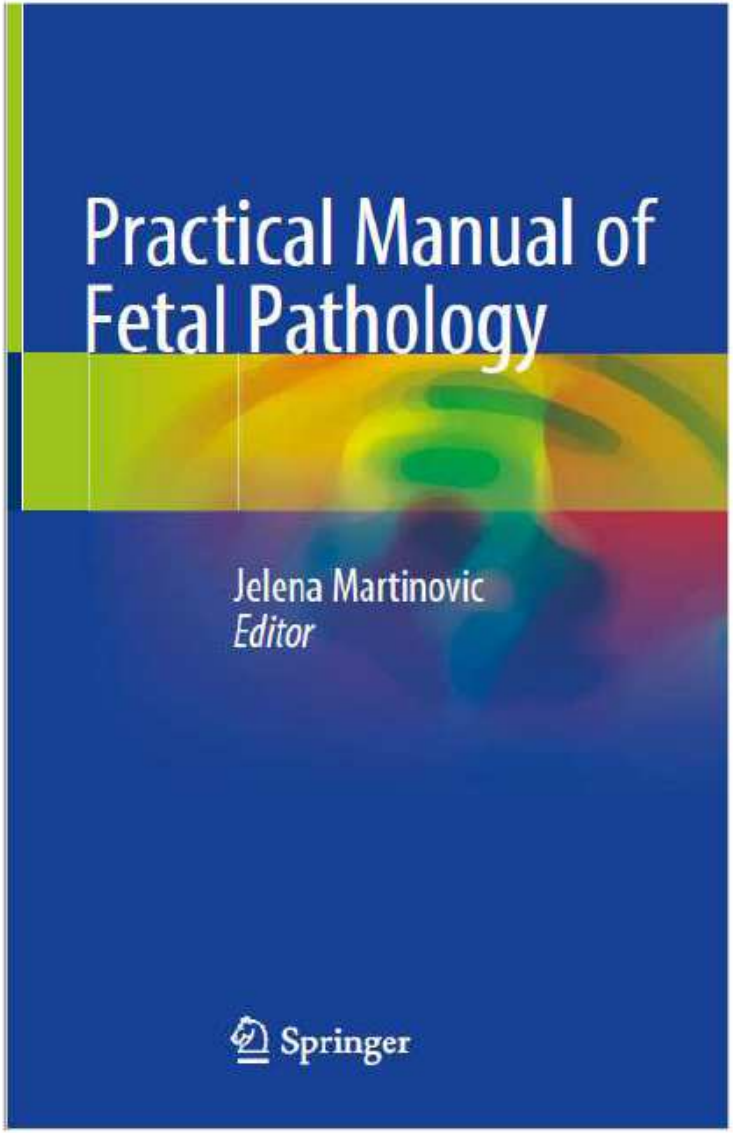

Jelena Martinovic
Editor

Practical Manual of Fetal Pathology

Foreword by John M. Opitz

Springer

This book provides a concise guide to fetal pathology and postnatal fetal examination.

The legal and ethical aspects of fetal examination are addressed, along with the modern practical approach to fetal malformations, oriented fetal autopsy, neuro-fetopathological examination, and pathology of the placenta.

Practical Manual of Fetal Pathology aims to evaluate recent advancements and the impact they have had on clinical practice.

This book is relevant to fetal and perinatal pathologists, geneticists, obstetricians, gynecologists, and pediatricians.

Foreword

On a Prefatory Note

Fetoplacental pathology is the last frontier of human biology and medicine given the appalling prenatal death rate of our species (>50%), much of which remains unexplored. By "fetoplacental" I understand the *fetus* from term to 57 days of gestation, the embryo from 56 days to fertilization, and the *placenta* as all trophic tissue at all stages, intact or in pieces, to be sorted from decidua and clots in the lab. And I do so in the hope that all of you are or will be working in services that cover *all* pregnancy stages without sequestering those up to 12 weeks of gestational age as "products of conception" into Surgical Pathology where they may receive only stepmotherly attention. And, finally I do so with the expectation and confidence that your place of work is not just a perfunctory service morgue but also an exciting classroom open to any and all advances in developmental biology, pathology, and genetics and a laboratory initiating research in all of these areas toward a better and deeper understanding of human ontogeny. Innumerable causes of prenatal death in humans are yet to be discovered—mutations, TADs, aneuploidies, infections, maternal-placental and epigenetic factors, teratogenic disruptors.

Thus, it is with great pleasure and profound satisfaction that I welcome the Martinovic Manual into life and action. Here is not only a technical *vade mecum* but a biology text by those whose eyes, minds, calipers, and scalpels have been and are guided by insight, decades-long experience, profound knowledge of their subject, and love of their "craft." A beloved, small, but world-renowned band of collaborators in this vineyard, who speak a familiar, universal language, eager to convey wisdom and experience, in practice, to teach, and to urge research. I had a similar experience a half century ago being instructed by an equal master as the Martinovic authors, Enid Gilbert in a 9-year apprenticeship with profound effect on my appreciation of that half of humanity never to nurse or to play with green, plastic dinosaurs. Even before Enid, I had the chance to meet the serious Edith Potter in Chicago: "...put some Prussian Blue on it Opitz!" leading to the discovery of lysosomal defects in Zellweger syndrome. Here I should just say *Vale*! and lay down my pen, but I am tempted to add a footnote on the origin of our discipline.

To this moment in time, developmental pathology has primarily struggled with *morphology*, form and formation, i.e., anatomy and embryology, on gross and

microscopic levels, normal and abnormal. Until suddenly, in the 1960s, our vision was marvelously focused and sharpened by *cytogenetics*, the pathology of aneuploidy seen in trophoblastic disease, monosomy X, trisomy-21, -13, -18, triploidy, etc., and the vast amount of *genetic* disease to be seen in CVS samples and POCs alone at, or shortly after the first missed period. So, as cytogenetics barged through the front door of developmental pathology, genetics tiptoed in through the backdoor to become our permanent bedfellow, initially aiding our understanding of gestational *physiology* and *metabolism* with a marvelous array of biochemical and histochemical tests, finally introducing us to *evolution*.

Our field of medicine and biology began very differently from what we now know as fetoplacental pathology, not (yet) as public service but as private instruction, not so much out of the needs of a discipline but of a single person, and not solely focused on humans, but the entire animal kingdom, a perspective we now have lost, sad-to-say. The times could not have been worse—Napoleon had devastated Europe (sort of), defeated Prussia, and occupied Halle closing its University. Nevertheless, Johann Friedrich Meckel Jr. (1798–1862) was able to study in Paris at the *Jardin des Plantes*, beneficiary from the vast natural history collections accumulated under Napoleon and, over 2 years, the collaboration with Cuvier, then Europe's most distinguished comparative anatomist, who, however, disdained evolutionary notions, embryos, and malformations, eagerly taken up by Meckel. His undisputed masterpiece, the *Handbuch der pathologischen Anatomie* (1812), has not been translated into English since 1831. In it, and his voluminous other writings, Meckel adumbrated not only meticulous dissection, preparation, and preservation (a few of his specimens still kept in the Anatomy Department of the University of Halle) but also the notions of:

- Primary malformations as defects of earliest development;
- Malformations as a result of delayed or incomplete ("inhibited") development;
- Multiple segregating anomalies not as coincidences but as causal complexes, in some cases as (now) evident autosomal recessive (Meckel syndrome) and in others as autosomal dominant (the Calleja family of Malta). Thus, Meckel is the father of modern syndromology and clearly knew pleiotropy for what it was;
- Corresponding structures and malformations in humans and other animals as forms of similarity, *analogie*, now homology; wonderful examples are his discussions of unilateral pulmonary agenesis in humans and lung development in "higher" and "lower" snakes; or of Meckel diverticulum as vestigial remnant of the amniote omphalomesenteric duct.
- More yet, Meckel correctly grasped the relationship between the development of the individual and that of the species, i.e., the concept of recapitulation later condensed by Haeckel (1866) into the better-known catch phrase of "ontogeny recapitulating phylogeny."

The fact that during our development we repeat what our direct progenitors and other members of our species have practiced successfully since time immemorial is intuitively obvious. But, repeat how? by inheritance; of what? *die formbildenden*

Elemente (Mendel 1865/1866)—the segregating morphogenetic elements. Elements that are the currency of evolution. Operating how? By natural selection, selection we see daily at autopsy and which has resulted not in what we could have become but what we did become by default—a very frail species indeed. What kinds of *Elemente*? Hereditary units made of DNA (Watson and Crick 1953) to serve as templates for development of individuals through transcription, translation, and replication and of species by mutation. *Elemente* now called genes, biochemical molecules that serve *all* species to resist death, are the basis of *all* organic form and function and, by their very nature, make *all* species more or less vulnerable to extinction and selection. Thus, it is the very same genes that were responsible for the evolution of spiders and of spider monkeys as metazoans, i.e., of animals with epithelia and organs, as the genes that made chimps and humans fellow primates, no supernatural intervention or explanation required.

Finally, we ask: What would paleontology be like without the Meckel cartilage and its evolutionary role in the formation of mandible, TM joint, and middle ear? Just think: trisomy 18 and hemifacial microsomia!

The road ahead for all of us pulling the faculty, student, and trainee wagons together is clear: effective knowledge of human anatomy, embryology, and genetics, and not only knowledge but understanding of the long recapitulatory argument mentioned above. Increasingly we will be receiving lab results stating plainly: mono- or biallelic mutation of gene X at site Y on chromosome Z (HSA or HSX, long or short arm), a sufficient causal explanation if also known or discovered in other "cases" with corresponding phenotype. What the lab test may also indicate in fine print is that gene X is "highly conserved in *C. difficile*, *E. coli*, *C. elegans*, *D. melanogaster*, *M. musculus*," etc.; in other words, it was present in LUCA over three billion years ago and has served life faithfully from prokaryote to eukaryote, from unicellular to multicellular organization, sea to land to air, and chordate to primate. The dead fetus before you, clearly human, unable to have resisted death in form, formation, or function, yet has so much to teach us as apparently successful phylogeny but failed ontogeny. The challenge to you may involve processes billions of years old, knowing for example that some one third of the protein-encoding genes that were present in LUCA 3.8 billon years ago (Weiss et al. 2016) are still present in humans (Martin, pers. comm. 2019).

On that journey, the authors of Martinovic will be your reliable guides.

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