Book Reviews

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Overgrowth Syndromes. By Michael Cohen, Jr.; Giovanni Neri; and Rosanna Weksberg. New York: Oxford University Press, 2002. Pp. 206. $85.

This timely, intriguing volume represents the collaborative efforts of three individuals at the forefront of overgrowth syndrome study: Dr. M. Michael Cohen, Jr.; Dr. Giovanni Neri; and Dr. Rosanna Weksberg. The book discusses a group of disorders resulting in large size at birth, excessive postnatal growth, or some combination of increased weight, increased length, and/or increased head circumference. In a number of these syndromes, there is not only somatic overgrowth but also a risk of neoplasia. With an increasing number of recognized overgrowth syndromes and significant recent advances in our understanding of the molecular mechanisms producing overgrowth, this is a welcome publication. Comprehensive works addressing this complex group of disorders have not previously existed.

As Dr. J. Bruce Beckwith notes in his insightful foreword to the book, new discoveries of the molecular processes at work in overgrowth syndromes, such as genomic imprinting in Beckwith-Wiedemann syndrome, have contributed to the recognition of similar processes in tumor growth. This book comprehensively couples detailed clinical information on overgrowth syndromes with current knowledge of their molecular biology. In spite of the complexity of the underlying molecular mechanisms of many of these syndromes, the authors have created a highly readable text which provides thorough, clearly presented explanations of their pathogenesis.

After an introductory overview, the next 12 chapters of the book are each devoted to one of the well-recognized overgrowth syndromes: Beckwith-Wiedemann syndrome; hemihyperplasia; Simpson-Golabi-Behmel syndrome; Perlman syndrome; Sotos syndrome; Weaver syndrome; Bannayan-Riley-Ruvalcaba syndrome; Proteus syndrome; Klippel-Trenaunay, Parkes Weber, and Sturge-Weber syndromes; Maffucci syndrome; neurofibromatosis; and fragile X syndrome. Additional chapters summarize chromosomal disorders with overgrowth, maternal and endocrine effects, nonsyndromal overgrowth, fetal hydrops, and other syndromes and conditions with overgrowth.

The organization of each chapter differs slightly, depending on the state of knowledge for each syndrome. Most chapters contain sections providing a historical perspective, epidemiology, etiology and molecular biology when known, growth and skeletal findings, clinical phenotype, diagnostic criteria, associated neoplasms, diagnostic studies, and differential diagnosis. When available, estimates of birth prevalence, growth curves, and final height attainment for the syndrome are included; this is certainly useful information not easily found elsewhere. Susceptibility to specific tumors, a key finding in many of the diverse conditions causing overgrowth, is highlighted throughout the book. The differential diagnoses are masterfully done and will be of great benefit to practitioners. They are both inclusive in syndromes listed and succinct in discussion of distinguishing features.

I found several chapters particularly well done. The Beckwith-Wiedemann syndrome chapter contains an excellent, understandable review of the complex genetic and epigenetic factors involved, as well as useful guidelines on postnatal patient evaluation. The exhaustive chapter on Proteus syndrome includes fascinating historical information and very detailed listings of uncommon and unusual clinical findings and neoplasms. The chapter on Klippel-Trenaunay, Parkes Weber, and Sturge-Weber syndromes is very helpful in clarifying terminology and in the classification of these disorders. The chapter on maternal and endocrine effects contains excellent discussions of infants of diabetic mothers and persistent hyperinsulinemic hypoglycemia of infancy, along with the interesting section on infants of psoriatic mothers. Included in the chapter, "Chromosomal Disorders and Overgrowth," are descriptions of Pallister-Killian syndrome (mosaic tetrasomy 12p) and several other chromosomal duplications and deletions. The chapter entitled, "Other Syndromes," includes several relatively rare but important conditions: Costello syndrome, macrocephaly-cutis marmorata syndrome, Cantú syndrome, Nevo syndrome, and Elejalde syndrome. The final chapter, "Miscellaneous Syndromes and Conditions with Overgrowth," provides brief, informative reviews of over 20 conditions, including some in which only a subset of patients show overgrowth.

Appearing throughout the book are the wonderful, highly detailed tables that are Dr. Cohen's trademark, some newly created and some carefully updated and adapted from previous publications. These useful tabular summaries permit ready access to an enormous volume of clinical information. Tables summarizing the types of tumors reported in each condition and the frequencies of their occurrence will be especially helpful to clinicians. The diagrammatic representations of molecular processes are very well done, notably those illustrating imprinting in Dr. Weksberg's chapter on Beckwith-Wiedemann syndrome, the putative role of GPC3 in Dr. Neri's chapter on Simpson-Golabi-Behmel syndrome, and the working model of the PTEN regulatory network in Dr. Cohen's chapter on Bannayan-Riley-Ruvalcaba syndrome. Most chapters feature outstanding illustrations of pathological findings. Excellent patient photographs appear in every chapter; particularly helpful are the photographs demonstrating the evolution of the facial phenotype in Beckwith-Wiedemann syndrome and the extensive photographic illustrations of Proteus syndrome.

Each chapter is very thoroughly referenced; the book contains over 1,000 references. The writing is excellent, interspersed with practical comments, pearls of wisdom, and occasional witticisms from the authors, making the book both enjoyable to read and exceedingly applicable in practice.

Overgrowth Syndromes is a unique, landmark book packed with information, compiled in expert fashion by these well-recognized authors. It will be an essential addition to the libraries of medical geneticists and dysmorphologists and a valuable resource for pediatricians, oncologists, hematologists, pediatric endocrinologists, pathologists, surgeons, dermatologists, nephrologists, radiologists, and molecular biologists.

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Genes and Mechanisms in Vertebrate Sex Determination. Edited by G. Scherer and M. Schmid. Basel: Birkhäuser Verlag, 2001. Pp. 205. $109.

The Genetics and Biology of Sex Determination. Novartis Foundation Symposium 244. Chichester: John Wiley and Sons, 2002. Pp. 265. $125.

What is uniquely valuable about these books that would make it worth owning, or at least reading, both? Those with a strong interest in that area of developmental biology pertaining to the evolution, genetics, endocrinology, development, and clinical aspects of sex determination and sex differentiation will find that, in spite of considerable overlap, these volumes complement each other in may ways, each bringing exceptionally valuable contributions. The Wiley book is, in all respects, a later and more up-to-date treatment.

The Birkhäuser volume consists of "updated and revised versions" of a series of articles published in the multiauthor review of *Genes and Mechanisms in Vertebrate Sex Determination* in *Cellular and Molecular Life Sciences* (1999, 55: 821–931). Susumu Ohno's final illness precluded revision of his paper; the review by Schmid and Steinlein is new. The editors are well known: Schmid (Würzburg), for his work in amphibian sex determination and sex differentiation, and Scherer (Freiburg), for his contributions to *SOX9* and the campomelic syndrome. The book is dedicated to Ohno, "whose contributions to the field of vertebrate sex determination have stimulated and inspired research in this field over many years." In addition to the preface, the book contains nine reviews: Ohno, "The One-to-Four Rule and Paralogues of Sex-Determining Genes"; Parker, Schimmer, and Schedl, "Genes Essential for Early Events in Gonadal Development"; Koopman, "*Sry, Sox9* and Mammalian Sex Determination"; Goodfellow and Camerino, "*DAX-1,* an 'Antitestis' Gene"; Pask and Graves, "Sex Chromosomes and Sex Determining Genes: Insights from Marsupials and Monotremes"; Clinton and Haines, "An Overview of Factors Influencing Sex Determination and Gonadal Development"; Pieau, Dorizzi, and Richard-Mercier, "Temperature-Dependent Sex Determination and Gonadal Differentiation in Reptiles"; Schmid and Steinlein, Sex Chromosomes, Sex-Linked Genes, and Sex Determination in the Vertebrate Class Amphibia"; and Baroiller and Guiguen, "Endocrine and Environmental Aspects of Sex Differentiation in Gonochoristic Fish."

In his review, Ohno was able to bring concrete evidence for his hypothesis, advanced in 1970, that gnathostomes "underwent two successive rounds of tetraploidization at their inception"; that is, that vertebrates are the octoploid descendants of an ancestor with a much simpler genome—hence, for example, our four paralogous *Hox* groups compared with the single *Hox* cluster in *Drosophila*, with a similar situation in the *Notch, Mef2, Ras, Egrl/Krox20, Gli, Src, Scr*-related, and *Jak* genes; the nuclear receptor family; and *Sox* genes.

Ohno, for one, was impressed by the antiquity of *SRY,* thought that it was worthwhile looking for its ancestor among the invertebrates, and concluded that it was not closely related to *Sox3*. For an answer and update, one must go to the Graves review in the Novartis volume (pp. 86–111, with discussion to p. 114). She concurs that *SRY* arose from (the X-linked) *Sox3* or *SRX* gene rather recently, since it is present only in mammals and marsupials and not in nonmammalian vertebrates (the monotremes).

In the Birkhäuser volume, the *Sry* and *Sox9* story is told in detail by Peter Koopman, with over 200 references, and will remain the definitive review of that subject for a long time.

Peter Goodfellow and Giovanna Camerino review their work and that of others on *DAX-1,* the antitestis gene, and point out the differences in function of that gene in mice and humans; absence of *DAX-1* in humans leading to congenital adrenal insufficiency and hypogonadotrophic hypogonadism; and, in mice, associated with normal gonadotropin levels. The concept of an antitestis effect of *DAX-1* in the development of the ovary recalls the pioneering concept of Witschi of corticomedullary antagonism ("anticorticin" and "antimedullarin") during gonadal differentiation. Indeed, most of Witschi's work is severely neglected by recent workers in the field, including the very idea that the initial gonad of vertebrates is bipotential, with cortex becoming ovary in females and medulla becoming testis in males.

The review by Andrew Pask and Jennifer Marshall Graves on the marsupial and monotreme sex chromosomes and sex-determining genes is a lovely introduction updated and amplified by Graves in the Novartis volume (pp. 86–110).

Clinicians may think that the rest of the reviews in the Birkhäuser volume on birds, reptiles, amphibians, and fish can be safely ignored because of lack of pertinence to clinical practice. Such a narrow view would deprive the reader so inclined of a huge amount of intellectual pleasure, a chance to reaffirm the perspective—no, the *fact*—that everything that develops has evolved and of some amazing comparative insights of direct clinical relevance. The most interesting of these, at least to this reader, is the del(9p) story. In males, such deletions may lead to male pseudohermaphroditism caused by deletion of the *DMRT1* gene—to date, the only sex-determining gene known