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

in birds, where the gene resides on the Z chromosome in a region homologous to a substantial portion of HAS 9p. *DMRT1* shows differential expression during gonadal embryogenesis of birds, mammals, and alligators; its *Drosophila* (*dsx*) and *Caenorhabditis elegans* (*mab-3*) homologs are directly involved in male sex development.

The sequential reference numbering system in the Birkhäuser book is a nuisance and makes it difficult to find references in the (nonalphabetical) bibliographies, but that and a certain lack of historical perspective are about the only criticisms I have of this otherwise highly interesting and most useful book.

The Wiley volume on the same subject is an equally interesting and useful book. It is the result of a Novartis (formerly Ciba) conference held in London in May 2001; thus, the information it contains is only 1 year old. Its advantage over the Birkhäuser book is the lively discussion following every presentation; these discussions cannot be skipped since they frequently bring out additional important points not made during the formal presentations. These Novartis conferences are always international events. The 2001 conference was no exception, with investigators represented from the United States, France, Spain, the United Kingdom, Italy, Australia, Japan, and Germany. The conference was chaired by the irrepressible Roger Short, from Melbourne, who commented on a certain preponderance of workers from Australia to the effect that "Sex 'Down Under' is done rather differently giving the rest of us 'much to learn from Gondwanaland about the evolution of sex.'" One wonders what inspired him to say in his introduction "that the somatic sex of the gonad is a secondary issue; it is germ cell sex that ultimately determines maleness or femaleness," something shown to be wrong by Witschi and others decades ago and challenged in a discussion by Paul Burgoyne.

Robin Lovell-Badge and his coworkers discuss sex-determining genes in mice, sans *DMRT,* and emphasize the critical role of *Sox9*. The functions of *WT1* and *Sox9* are reviewed by Guo and his coworkers, from Newcastle-upon-Tyne, with Peter Koopman, of Brisbane, leading the discussion of the mechanism of action of SRY. In a brief but most useful contribution, Eric Vilain, of UCLA, reviews some anomalies of human sexual development, mostly from the perspective of the genes involved in early gonadal development. Vincent Harley, of Melbourne, analyzes some of the molecular complexities of *SRY* and *Sox9,* and the multicenter team of Suzuki et al. addresses concerted regulation of gonad differentiation by transcription and growth factors. Jennifer Graves, of Canberra, brings the evolution of the *SRY* gene up to date, and Andrew Sinclair et al., of Melbourne, present a most informative comparative analysis of vertebrate sex determination, with discussion ranging freely over the monogonadal nature of bird and monotreme females, left ovarian development in human and mouse hermaphrodites, bird sex reversal (a hen in one and a rooster in the next season), and 5α-reductase deficiency in humans.

In his paper, "Invertebrates May Not Be So Different after All," David Zarkower, of Minneapolis, discusses an example of apparent conservation of a very ancient sex-determining system: the *dsx* (double sex) gene of *Drosophila,* male abnormal 3 (*mab-3*) gene in *C. elegans,* and their *DMRT1/Dmrt1* homologs in mice, humans, birds, fish, and reptiles.

Unique to the Wiley book is a valuable summary of the hormonal control of sexual development by Renfree et al., from Melbourne and Houston, contrasting, among others, the differences between eutherians and marsupials. Jamin et al., from the lab of Richard Behringer, in Houston, review the MIS (anti-Müllerian hormone) story, with Nathalie Josso, the pioneer of AMH studies, providing valuable commentary.

To me, the gold-star paper in this volume is the extraordinary work by Russell Fernald, of Stanford, on the influence of social status on brain and gonadal development in the cichlid fishes from Lake Tanganyika, something I will leave for the reader to discover and that taught me more than most of the other contributions in either volume.

In "The Battle of the Sexes: Opposing Pathways in Sex Determination," Yao and other collaborators of Blanche Capel, of Duke University, show that it is indeed possible to convert XX gonads into testes in mammals and that it is the autonomous entry of germ cell into meiosis that initiates the ovarian pathway and blocks testis development. Testis development in response to SRY "opposes" this pathway by initiating cord formation prior to meiosis and sequestering germ cells inside cords, arresting them in mitosis. The ghost of Emil Witschi must have been happy to hear this beautiful work.

A valuable discussion of hermaphroditism precedes the authoritative paper by Brian Charlesworth, of Edinburgh, on the evolution of chromosomal sex determination, the only review in either book to deal with the population genetical considerations underlying the evolution of bisexuality.

Gerd Scherer reviews the "Molecular Genetic Jigsaw Puzzle of Vertebrate Sex Determination and Its Missing Pieces" with a table of 14 genes known in 2001 and updating Peter Koopman's most useful diagram (from the Birkhäuser volume) on their role in male and female gonadal/genital development. Koopman and coworkers, in the last paper in this volume, point the way to the future by reviewing the application of expression-based strategies for the discovery of genes involved in gonadal development. Their use of high-throughput, array-based expression screening has already led to the identification of a new gene involved in the migration of mesonephric cells into the male genital ridges.

Neither book has much to say about genetic defects of sex differentiation, such as androgen resistance or 5α-reductase deficiency. Except for *Sox9* and the campomelic story, few of the dozens of other syndromes with defects of sex differentiation (*ATRX, GBBB/MID1, DHTR7/RSH,* or *SLO* syndrome, etc., etc.) are mentioned or discussed, surely a fertile field for further investigations.

Nevertheless, both books are recommended as the best introductions to a fascinating field which has given biology thought for over 2,500 years, since the days of Aristotle.

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