impact on biology. To be fair, these research areas are still in their infancy and will have to mature considerably before their informatics textbooks can be written.

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Humans as Model Organisms

Transcription Factors and Human Disease
Oxford Monographs on Medical Genetics, No. 37
By Gregg L. Semenza
Oxford: Oxford University Press. (1998). 368 pp. $49.95

Since the golden age of phage and bacterial genetics, the power of genetic mutants to elucidate basic biochemical and developmental pathways has been self-evident. In the time since, countless mutations, ranging from behavioral to developmental to physiologic have been identified in organisms as diverse as yeast, worms, flies, and fish. This trend has been further facilitated by the current ascendancy of mouse molecular genetics. Yet the argument can be made that, among all organisms, the human remains the species in which the most sophisticated armamentarium of analytical and phenotypic analyses can be brought to bear. In addition, a pragmatic aspect to the analysis of human mutant phenotypes is their relevance to human disease. It is perhaps with these premises in mind that *Transcription Factors and Human Disease*, by G. L. Semenza, has been prepared.

The text is divided into two sections, entitled "Transcriptional Regulation" and "Transcriptional Pathophysiology." The first presents a survey of gene expression, transcriptional regulation, and *cis*-acting transcriptional regulatory elements. Chapters 1 and 2, dealing with transcription initiation, promoter structure, enhancers, chromatin looping, and negative regulatory elements, are rather perfunctory. However, following this introductory material is a remarkably detailed chapter on *trans*-acting factors, subdivided into discussions of activators, coactivators, architectural factors, repressors and corepressors, chromatin remodeling, and transcription elongation factors. Some of the material, for example, the discussion of TAFs, suffers from the complex and yet incompletely understood relationships between these different factors. And, although the situation will probably change, among the components of the basal transcription apparatus, only mutations in one of them, XPB/ERCC3, a subunit of TFIIH, have been associated with human disease (Xeroderma pigmentosum B and Cockayne syndrome). In addition, the work on multiprotein transcription complexes, although well developed, could be further supported by discussing in more detail the work on the enhanceosome, as revealed by studies on the transcriptional regulation of interferon-β expression. Nonetheless, this chapter, the last in the "Transcriptional Regulation" section, represents as complete and scholarly a review at a general level as currently exists.

The book's second section, "Transcriptional Pathophysiology," commences with a review of mutations in *cis*-acting transcriptional regulatory elements. Some of this material is old hat: promoter mutations in the β-globin promoter in thalassemia, or in the *F9* promoter encoding Factor IX in hemophilia B Leyden. But it can be fairly argued that information of this sort belongs in this text. A fascinating example is the acquisition of promoter mutations in the *DARC* gene that encodes the Duffy antigen that also serves as a receptor for the malarial parasite *Plasmodium vivax*. These mutations are prevalent at high frequency in West Africa where malaria is endemic, providing an example whereby mutations influencing transcription also serve as disease modifiers. Other examples remain unproven, such as the notion that the trinucleotide repeat expansion in the Fragile X syndrome gene *FMR1* interferes with a *cis*-acting regulatory element. However, their inclusion does serve to illustrate the diversity of mechanisms by which the transcriptional control of gene expression can be disrupted to produce a phenotype.

The most useful chapters of the book are those that follow, organized by transcription factor family, e.g., nuclear receptors, other Zn finger proteins, Pax, bHLH, homeodomain, HMG, and POU proteins. These chapters deal with transcription factor families in the context of some 40 different human mutational syndromes. The information on syndromes such as Rieger, Denys-Drash, Waardenburg (type 1–3), Aniridia, and Hand–Foot Genital, representing mutations in *PITX1*, *WT1*, *PAX3* and *MITF*, *PAX6* and *HOXA13*, respectively, is well presented and concise and accurately summarizes the present level of understanding about the individual gene products and about phenotype–genotype correlations. A particularly nice feature of this portion of the book is the integration of instructive results from other organisms, mice in particular. Another attractive feature is the numbers accompanying each syndrome that facilitate cross-reference to Online Mendelian Inheritance in Man (OMIM; http://www.nih.gov/omim). Students of human biology will thus find this material accessible, useful, and remarkably thorough—although inevitably outdated. Given the current pace at which human disease–producing mutations are being identified and the fact that subsequent editions of other volumes in the *Oxford Monographs* series have appeared, future editions of this work would seem to be in order.

As with any well-prepared treatise, this work raises as many interesting questions as it answers. Why, for example, should mutations involving genes that function widely in transcriptional regulation—such as *XH2* and *CBP*—result in highly specific developmental defects? Mutations in XH2, a widely expressed helicase thought to regulate transcription globally, result in the ATR-X syndrome, defined by X-linked α-thalassemia, facial and genital abnormalities, and mental retardation. The coactivator CBP participates in a plethora of important

transcriptional events, including not only its named function as a coactivator for the phosphorylated form of CREB (cAMP response element–binding protein), but also the regulation of histone acetylation. Yet while inhibition of expression of a *C. elegans* CBP homolog results in a complete absence of somatic morphogenesis, intragenic mutations in human CBP are associated with a comparatively restricted phenotype, Rubinstein-Taybi syndrome, a dysmorphosis characterized by specific limb and craniofacial defects and mental retardation. Since these genes are members of multigene families—CBP shares homology with another coactivator, P300, while XH2 is a member of the helicase superfamily—their restricted mutant phenotypes might be explained on the basis of functional redundancy. What seems equally likely, however—if unpleasantly more complex—is that it is the function of the gene product in the context of the specific biology of the organism that dictates whether and what identifiable phenotype will result.

Interestingly, Rubinstein-Taybi syndrome has been associated at low frequency with a variety of other congenital malformations, raising the possibility that the phenotypic expression of this disease results from polymorphic differences in the expression levels of other genes whose products interact with CBP. In the future, it can be anticipated that the identification of disease producing genes that must interact in specific allelic combinations to produce morbid phenotypes will further underscore the utility of the human as a model organism for understanding complex polygenic traits, such as intelligence, blood pressure, and disease susceptibility.

What are the practical consequences of the continued delineation of human transcription factor diseases? A potential answer is provided in the book's last chapter, entitled "Epigenetic Mechanisms." This chapter deals with the well-known propensity of teratogens such as retinoic acid and ethanol to induce congenital birth defects that phenotypically resemble those observed in some transcription factor diseases. Although their teratogenic mechanisms are poorly understood, the idea that epigenetic factors converge on basic transcriptional regulatory pathways during fetal development is highly attractive. Studies have shown, for example, that prenatal folate significantly reduces the incidence of neural tube defects such as spina bifida and anencephaly; as a result, the U.S. Food and Drug Administration now requires fortification of enriched grain foods with folic acid. Provocatively, a mouse mutant deficient for the homeodomain transcription factor Cart1 exhibits anencephaly, and the incidence of this neural tube defect is also strongly suppressed by prenatal folate. Thus, knowledge of the transcriptional regulatory pathways that govern human development may someday make it possible to understand how factors such as folate work, and to devise new strategies for the prevention of birth defects.

Another question, encouraged by the book's title, is whether mutations in genes encoding transcription factors are any more likely to cause developmental malformation syndromes than genes encoding other factors. In the preface, the author implies that this might be so, since transcription factors in general are thought to regulate the expression of multiple downstream genes. Yet the same argument can be made about the signal transduction pathways that growth factors activate. In fact, a survey of OMIM reveals that of the human genetic diseases for which genes are identified, only a small minority are caused by mutations in genes encoding transcription factors. While the restricted focus of this work on transcription factors is pragmatic, it is also thus somewhat contrived. For example, the text describes the involvement of the *MSX2* homeobox gene in Boston-type craniosynostosis, a disorder characterized by premature fusion of the sutures of the newborn skull. The more frequent and better-characterized craniosynostosis syndromes, however, are due to mutations in three of the FGF receptor genes. Left unexplored is what relation, if any, exists between FGF signaling and MSX2 in sutural biology. Ideally, the molecular function of transcription factors is best understood in the context of their biologic function, and vice versa.

Currently, the number of human genetic diseases listed in OMIM exceeds 10,000. As more and more disease-producing genes are identified, an attractive prospect for the future is their integration—whether they encode transcription factors or not—into specific pathways based on the analysis of their respective mutant phenotypes. Of course, studies in humans are necessarily limited in their potential for embryologic and genetic investigation, but they do provide a powerful starting point. Although this book is useful, left unconnected for the moment is the link between its first and second sections, between molecular function and an understanding of organismal function. At present, these sections can only cross-refer to one another. One can imagine, however, that future editions will begin to bridge this gap.

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DNA Repair in the 1990s

DNA Damage and Repair
Volume 1: DNA Repair in Prokaryotes and Lower Eukaryotes
Volume 2: DNA Repair in Higher Eukaryotes
Edited by Jac A. Nickoloff and Merl F. Hoekstra
Totowa, NJ: Humana Press (1998). Vol. 1, 626 pp. $125.00; Vol. 2, 639 pp. $125.00

A Dallas Cowboys linebacker intercepted a pass as a rookie and he made his second interception a decade later. When he was asked to comment about this long hiatus between the two interceptions he is reported to have said that everyone was entitled to an off decade. It appears that the field of DNA repair followed the same philosophy. After several momentous discoveries, which laid the foundation of the discipline in the 1960s, the repair community had an off decade lasting from about 1968 until 1977. In the 1960s the first known repair pathways were characterized, and it was shown that