

Book Reviews

Angiogenesis in Health and Disease: Basic Mechanisms and Clinical Applications, Gabor M. Rubanyi, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016-0602, <http://www.dekker.com>, 1999, xvii, 560 pp., illustrations, \$195.00.

In the Old Testament, the essence of life was to be found in the blood of man and beast. If true, then the bearer of life to each tissue must be the intricate system of capillaries, arteries and veins comprising the blood vascular system. The authors of *Angiogenesis in Health and Disease* are to be congratulated in remaining true to the title and providing an excellent overview of the basic mechanisms regulating normal and abnormal vessel development and the clinical applications that have evolved as a result of our improved understanding of angiogenesis. The material is introduced with an excellent overview of vascular development. The angiogenic growth factors and their receptors and other novel angiogenic gene products follow. A series of chapters devoted to the description of experimental animal models of normal and abnormal angiogenesis precedes the final section of the book summarizing the use of both angiogenic and anti-angiogenic strategies for treatment of human diseases.

The molecular events involved in the three phases of embryonic vasculogenesis, the process of the formation of the primordia of blood vessels, are contrasted with those processes regulating angiogenesis in the first chapter of this book. The schematic outline of the steps of vasculogenesis and early angiogenesis is expertly delivered and summarized in a singular figure. Angiogenesis, the formation of new capillary vessels from a preexisting capillary bed, is contrasted in Chapter 2 with arteriogenesis, the *in situ* growth of muscular collateral arteries in response to occlusion of an artery. Though the molecular mechanisms modulating arteriogenesis remain unclear, the morphologic phases of arterial vascular remodeling are well delineated. Chapters 3 and 4 comprehensively review the roles of vascular endothelial growth factor and the fibroblast growth factors and their cognate receptors in angiogenesis. The description of the pivotal roles played by vascular endothelial growth factor during embryonic vasculogenesis and in the pathophysiologic angiogenesis associated with tumor growth or as a result of vessel damage in diabetes mellitus are particularly interesting. The material in Chapter 5 is apparently placed to highlight the clinical correlation of human disease with abnormalities in some of the receptor tyrosine kinases regulating endothelial growth and vessel development. Recent information suggests a role for mutations in the TIE-2 receptor tyrosine kinase and abnormal intracellular signaling resulting in venous malformations. More attention to the description of the intracellular signaling events following TIE-2 activation would have clarified the hypothesis proposed to establish the role of endothelial receptor tyrosine kinase mutations and anomalous vascular development. The figure depicting the hypothesis is quite helpful. Chapters 6–11 are comprised of interesting well-written reviews of the roles of selected molecules regulating the angiogenic cascade. The role of endothelial differentiation 1 gene in mediating endothelial morphogenetic responses to circulating bioactive lipids and the role of hypoxia inducible factor-1 α in

mediating endothelial transcriptional responses to hypoxia were exceptional. Evidence to support a role of estrogen as a modulator of endothelial cell function and angiogenesis is concisely summarized in Chapter 12. Chapters 13–16 provide clear descriptions of the role of nitric oxide, oxygen, and reactive oxygen intermediates in angiogenesis. The above chapters comprise the first portion of the book which has been focused on informing the reader of the molecular events regulating angiogenesis.

The subsequent chapters focus on understanding the *in vivo* regulation of angiogenesis in a variety of experimentally induced or naturally acquired pathophysiologic disorders. *In vitro* and *in vivo* models of angiogenesis are introduced in Chapters 19–20. The use of tumor bearing animal models has led to the discovery of numerous anti-angiogenic molecules. Early clinical trials testing the safety of anti-angiogenic molecules such as thalidomide, CM101 (complex polysaccharide from group B β -hemolytic *Streptococcus*), and TNP-470 (a synthetic angiostatic antibiotic) are reviewed in Chapters 24–26. Potential roles of angiogenic molecules in the pathogenesis of human inflammatory states are described in Chapters 27–29. The book concludes by reviewing recent clinical and experimental studies suggesting that certain angiogenic molecules may serve as therapeutic molecules in improving blood vessel formation in a variety of ischemic states. These final chapters serve as a fitting culmination to this overall excellent overview of normal and abnormal angiogenesis. This book is written for scientists in the field of angiogenesis as well as interested health care professionals seeking a more fundamental understanding of blood vessel development.

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Protein Formulation and Delivery (Drugs and the Pharmaceutical Sciences, Volume 99), Eugene J. McNally, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, 1999. viii, 262 pp., illustrations, \$150.00.

The book starts with a brief overview of protein formulation and delivery. Then, the basic aspects of protein physical and chemical stabilities, and the appropriate methods to use for stability testing are reviewed. Next the critical importance of thorough preformulation studies is emphasized. Then, chapters deal with solution formulation development and the lyophilization process. Finally, the drug delivery section focuses primarily on pulmonary delivery and sustained delivery from microspheres.

As noted by the Editor, this book was written to assist the pharmaceutical scientist involved in the protein formulation and delivery processes. However, it will also be of use to students doing thesis research in these areas. Of particular value to the reader (especially those new to the field) are numerous insights into critical practical issues that impact the development of protein therapeutic products. The theoretical bases for protein

degradation, the use of appropriate analytical methods, liquid formulation development, and the delivery issues are briefly, but well explained. The lyophilization process is described in detail. However, it would have been helpful to have more information on the rationale for choosing stabilizing excipients for lyophilized formulations and on the critical physical parameters that dictate solid-state protein stability. Of course, such information is available elsewhere in reviews and books.

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Peptide and Protein Drug Analysis, Ronald E. Reid, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, 2000. xii, 885 pp., illustrations, \$235.00.

Overall, this is an excellent book covering all aspects of peptide and protein chemistry, structure and analysis. In fact, the book offers more as the title suggests, as not only drugs are considered. Moreover, through chapters on synthesis, folding, computational methods, and bioinformatics the scope of the book has clearly expanded beyond conventional "analysis." In the whole book I have only found two chapters which were not quite satisfactory, Chapters 2 (by Sawyer) and 16 (by Garner) (see also below). Especially, the mass spectrometry techniques should have been covered in more detail as they are developing so rapidly and will need to become routine for many peptide and protein researchers in the very near future. The organization of the book, starting with theoretical concepts followed by analytical methodology, is very appealing and I have had great pleasure reading this volume with the only two exceptions mentioned above.

The first ten chapters, in the section *Strategies*, deal with more theoretical aspects of peptide and protein structure, folding, synthesis, stability and modeling. In Chapter 1, Reid and Franchini give an excellent overview on all aspects of protein structure and the *ab initio* design of proteins or protein domains. The reader is introduced in a logical fashion to all important structural motifs of proteins, the individual parameters which contribute to their stability, and the amino acid compositions which are most frequently found in the respective motifs. This article is accompanied by an excellent reference list updated until 1997. The only weakness of this article is the sometimes poor reproduction of some of the Figures, e.g., Figures 7, 9, 16, 29, 35 and 36 which may be the result of copying color Figures. In Chapter 2, Sawyer reviews concepts and applications of peptidomimetics and nonpeptide drugs. Especially, the applications illustrated in Figures 7 and 8 will help the novice to understand how nonpeptide drugs are developed based on comparison of substructural elements. The vast number of structures which have been discovered are impressive, and the new approaches leading to increased speed of discovery (e.g., the various modes of combinatorial chemistry) are summarized well. The article should have been proofread in more detail as there are a number of errors (spelling, wrong number of Figure, a 10-membered intramolecular hydrogen bond between amino acid residues i and $i + 4$ in a β -turn, etc.). It also seems that

some of the Figures are reproduced from FAX transmissions. Chapter 3, by Munro and Taylor, gives a well written brief synopsis on software developments for the prediction of protein structure, ending with the fascinating example where predicted and experimental (NMR) structure of the protein NK-lysin were fairly superimposable. In its brevity, the article will not teach predictive tools to the beginner, but the www addresses supplied with most of the covered algorithms, together with the references (updated until 1997), will be very helpful to get started. In Chapter 4, Remmer and Fields guide the reader through the large number of possible routes in solid phase peptide synthesis (SPPS), covering all aspects from the importance of the physical properties of the resins, the optimization of synthetic protocols, to the final cleavage and purification steps of the peptide product. The article reads well, supplies an excellent reference list and constitutes a suitable introduction to Chapter 5, where Cotton et al. review recent progresses in the chemical synthesis of proteins. Especially, the developments in convergent protein synthesis using novel enzymatic or chemical ligation mechanisms are interesting, and this well-written article will fascinate also readers new to this field. These novel methods of protein synthesis, offer the possibility of introducing unnatural amino acids into proteins, as summarized by Lesley in Chapter 6. An important aspect of this article is that not only the potential but also the various potential problems of the described methods are illustrated. In Chapter 7, Winston and Fitzgerald review the various modes of combinatorial chemistry, specific encoding strategies, and give a series of illustrative examples where combinatorial chemistry has provided fascinating and unexpected results, for example in the identification of high-affinity ligands of proteins. It would have been interesting to see not only successful examples but also to obtain some more information on potential problems associated with combinatorial synthesis, the isolation, and the identification of the specific "hits". Chapter 8, by Strickland et al., deals with theoretical and practical aspects of protein folding. Correct folding is an important problem associated with the production of recombinant protein pharmaceuticals. However, in particular the unfolding of native proteins is also a special problem of the chemical and physical stability of proteins, summarized by Violand and Siegel in Chapter 9. Bioinformatics is the topic of Chapter 10, by Li and Robson, which nicely summarizes current developments and applications as well as future necessities of this emerging technology.

The next sections deal with the measurement of certain protein properties such as sequence and integrity, functional activity, and structure. In the section *Chemical Analysis*, Aguilar (Chapter 11) gives a thorough review over different modes of HPLC available for peptide and protein separation and analysis. Munro et al. (Chapter 12) illustrate the power of capillary electrophoresis (CE). Especially the developments in coating technology have opened more possibilities for effective peptide and protein separation by CE. Moreover, microchip CE will provide opportunities for the development of diagnostic kits. Gel electrophoresis is still the workhorse for convenient analysis proteins from biological matrices. Especially, in combination with MALDI-TOF mass spectrometry, 2D-gel electrophoresis has found wide application in modern proteomics research. These aspects, as well as many technological details on gel electrophoresis, are nicely reviewed by Dunn in Chapter 13. Important detail of proteins, whether obtained from tissue or

as recombinant proteins, are potential glycosylation patterns. In Chapter 14, Jenkins et al. summarize various aspects of glycosylation; however, the article would have benefited from a more in-depth discussion of analytical strategies. In contrast, sequencing strategies are discussed in quite detail in Chapter 15 by Lu et al. Quite unsatisfactory is the section on mass spectrometry by Garner et al. (Chapter 16). This technique has revolutionized modern peptide and protein research especially through the development of electrospray ionization and MALDI-TOF MS. Yet, the sections on ESI and MALDI-TOF are quite brief, in essence shorter than the sections on the older methods electron impact and chemical ionization MS. There are so many new applications of MALDI-TOF MS that this technique would have deserved broader coverage, for example, a better description of delayed extraction, reflectron and postsource decay methods.

Chapters 17–21 in the section *Functional Analysis* are all well written and of general use for advanced scientists as well as novices in the field. The final section of the book deals with the *Structural Analysis* of peptides and proteins. The first two chapters (22 and 23) summarize methods and applications of NMR spectroscopy. These articles are well designed and reflect the importance of this technique in protein structural analysis. In Chapter 24, Anderson underlines the complementarity of CD and FTIR to NMR and x-ray structural analysis, and gives a thorough review on the various structural elements recognized by these techniques. In Chapter 25, Marsh introduces the reader to the various application of electron spin resonance spectroscopy (ESR) as a dynamic technique to monitor protein dynamics (e.g., rotational mobility) and conformation as well as protein binding. The UV-visible and fluorescence spectroscopy techniques and applications are reviewed in Chapter 26 by Anantharamaiah et al. UV-visible spectroscopy serves as a tool to determine protein concentration, purity and binding equilibria. More detailed structural information is available from time-resolved fluorescence measurements such as fluorescence resonance energy transfer (FRET). Finally, in Chapter 27 Eisenberg gives an excellent account on theoretical aspects of ultracentrifugation and light-scattering techniques.

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In Quest of Tomorrow's Medicines, by Jürgen Drews, Springer-Verlag New York, Inc., 175 Fifth Avenue, New York, NY 10010, 1999, vi, 272 pp., illustrations, \$29.95.

Drugs play a central role in medical practice. Drugs are not everything in medicine, but there would be no modern medicine without them. This is one of the reasons why the pharmaceutical industry has been growing so much throughout the history, especially in the modern era. This book provides extensive diagnosis of the current pharmaceutical industry from the historical point of view to provide a glimpse into the future of the drug industry. The pharmaceutical industry, that has its origin in the dye industry, prospered based on the basic research provided by chemistry (for synthesis and

analysis), modern pharmacology (for establishing dosage-effect relationships) and biochemistry (for the isolation of enzymes and the concept of receptors). Today, the pharmaceutical industry is at a crossroad of a traditional way for discovering low molecular weight drugs and a new way of discovering protein drugs by molecular biology. The outcome of the research based on molecular biology would be different from that of traditional drug discovery in that the molecular biological research is generating new therapeutic concepts. Genetic research arising from molecular biology has made it possible to identify and understand pathogenic genes and gene products.

The general trend in the current pharmaceutical industry is that the number of new introductions of pharmaceutical compounds becomes smaller every year since 1985. If this trend continues, the pharmaceutical industry as a whole cannot produce any significant growth, especially when the average cost of finding and developing a new drug is in the range of \$350–500 million. The book indicates that the pharmaceutical industry is finding a way of increasing the output by acquiring (complementary) skills, functions, and products through mergers and acquisitions. This may be an acceptable practice, but it has undesirable side effects. As the company becomes larger by mergers, it will have to generate at least one “blockbuster” drug every year to sustain, and it may not be easy. Furthermore, the book points out that the inevitable downsizing after mega-mergers results in a culture that does not provide environment for the basic research. The book continues to point out that, unfortunately, the pharmaceutical industry has created environment that selects against scientific individuality, creativity, and originality in favor of consensus, getting along, subordination, and a task-oriented mindset. This leads to an exodus of first-rate scientists to the universe of discovery companies, i.e., biotechnology companies. The biotechnology companies is lacking the methods and capital for product development while the pharmaceutical industry has both. This means that the pharmaceutical industry has a chance to maintain its own role as an innovator through strategic alliances with smaller, technologically motivated biotechnology firms. The book depicts the biotechnology firms as the future supplier of the ideas, technologies, and new products, while the pharmaceutical firms as the other extreme. This is a far cry from the roles that mighty pharmaceutical companies have played until now. The book concludes that the drug research in the future will involve many partners with the biotechnology industry playing the most important role of discovering new drugs. The classical pharmaceutical firms will function only as developers with the help of contract research organizations, as manufacturers, and as distributors.

This is an absorbing book that is hard to stop reading. There are many interesting stories, such as thalidomide affair, that describe serious consequences resulting from a series of unintentional, and possibly intentional, lack of good laboratory practices. Knowing such details will, hopefully, prevent similar mistakes in the future. The book is a real page-turner with a lot of interesting stories, detailed analysis of the current pharmaceutical industry, and insightful visions of the future. The author of the book has extensive practical experiences in drug development, and his expertise and knowledge make this book very informative. Considering tremendous pressure that

the pharmaceutical industry is receiving nowadays from governments, managed health care organizations, patients, and Wall Street, one can easily understand that the future of the pharmaceutical industry will not be the same. If the changes and turmoils happening in the pharmaceutical industry today are any indication of what may yet to come, the book will serve as a reliable source for predicting the future of the drug makers. As the author mentioned many times in the book, however, predicting the future is not an easy thing to do. It only relies on facts available today and even the best prediction would be reliable only for the next several or ten years. If this book served as a time machine traveling to the future of the pharmaceutical industry, those in the pharmaceutical industry should feel fortunate enough to be able to do something now to alter the course of the future of the industry. Only if it is necessary at all.

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Books Received

Biomaterials

Biomaterials Regulating Cell Function and Tissue Development, Materials Research Society Symposium Proceedings Volume 530, Robert C. Thomson, David J. Mooney, Kevin E. Healy, Yoshito Ikada, Antonios G. Mikos, Eds., Materials Research Society, Customer Services Department, 506 Keystone Drive, Warrendale, PA 15086, <http://www.mrs.org/>, 1998, ix, 119 pp., illustrations, \$79.00.

Computational and Mathematical Models of Microstructural Evolution, Materials Research Society Symposium Proceedings Volume 529, Jeffrey W. Bullard, Long-Qing Chen, Rajiv K. Kalia, A. Marshall Stoneham, Eds., Materials Research Society, Customer Services Department, 506 Keystone Drive, Warrendale, PA 15086, <http://www.mrs.org/>, 1998, xi, 183 pp., illustrations, \$76.00.

Polysaccharides. Structural Diversity and Functional Versatility, Severian Dumitriu, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, 1999, xiii, 1168 pp., illustrations, \$250.00.

Biological Interfaces

Protein Architecture: Interfacing Molecular Assemblies and Immobilization Biotechnology, Yuri Lvov and Helmut M \ddot{o} hwald, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016-0602, <http://www.dekker.com>, 1999, x, 416 pp., illustrations, \$175.00.

Interfacial Dynamics, Surfactant Science Series/88, Nikola Kalay, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016-0602, <http://www.dekker.com>, 1999, 760 pp., illustrations, \$195.00.

Physical Chemistry of Biological Interfaces, Adam Baszkin and Willem Norde, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016-0602, <http://www.dekker.com>, 1999, ix, 848 pp., illustrations, \$225.00.

Pharmaceutics

Handbook of Pharmaceutical Excipients, Third Edition, Arthur H. Kippe, Ed., American Pharmaceutical Association, 2215 Constitution Avenue, NW, Washington, DC 20037-2985, <http://www.aphanet.org>, 1999, xx, 665 pp., illustrations, \$295.00.

Excipient Toxicity and Safety, Drugs and the Pharmaceutical Sciences, Volume 103, Myra L. Weiner and Lois A. Kotkoskie, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602, <http://www.dekker.com/>, 1999, x, illustrations, \$165.00.

Transport Processes in Pharmaceutical Systems, Drugs and the Pharmaceutical Sciences, Volume 102, Gordon L. Amidon, Ping I. Lee and Elizabeth M. Topp, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, <http://www.dekker.com>, 2000, ix, 727 pp., illustrations, \$225.00.

Pharmaceutical Dosage Forms and Drug Delivery Systems. Seventh Edition, Howard C. Ansel, Loyd V. Allen, Jr., and Nicholas G. Popovich, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436, 1999, x, 595 pp., illustrations, paper, \$48.00.

Reference Books

Handbook of Biochemical Kinetics, Daniel L. Purich and R. Donald Allison, Eds., Academic Press, A Division of Harcourt Brace & Company, 525 B Street, Suite 1900, San Diego, CA 92101-4495, <http://www.apnet.com>, 2000, 788 pp., illustrations, \$150.00.

Martindale. The Complete Drug Reference, Thirty-second Edition, Kathleen Parfitt, Ed., The Pharmaceutical Press, 1 Lambeth High Street, London SE1 7JN, UK, 1999, xii, 2315 pp., illustrations, \$299.00.

Traditional Chinese Medicines, Molecular structures, natural sources, and applications, by X. Yan, J. Zhou, and G. Xie, Ashgate Publishing Company, Old Post Road, Brookfield, VT 05036, www.ashgatechem.com, 2000, xix, illustrations, 1024 pp., \$295.00.

Cosmetic Regulation in a Competitive Environment, Norman F. Estrin and James M. Akerson, Eds., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 1006-0602, <http://www.dekker.com/>, 1999, xvi, 473 pp., illustrations, \$195.00.

Therapeutics

Cholesterol-Lowering Therapy: Evaluation of Clinical Trial Evidence, Scott M. Grundy, Ed., Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016-0602, <http://www.dekker.com>, 1999, xv, 336 pp., illustrations, \$150.00.

Caffeine. Fact & Fallacy, by Augustine S. Aruna, Global Publishing Network, P.O. Box 850439, New Orleans, LA 70185, <http://vsp.wpg.net/IN/GLOBALPUBLISHING>, 1999, 80 pp., illustrations, \$18.95.

Pathology for the Health-Related Professions, Second Edition, by Ivan Damjanov, W.B. Saunders Company, A Division of Harcourt Brace & Company, the Curtis Center, Independence

Square West, Philadelphia, PA 19106, 2000, xviii, 545 pp., illustrations, paper, \$52.00.

Gibaldi's Drug Therapy 2000, A Critical Review of Therapeutics, by Milo Gibaldi, McGraw-Hill, 1221 Avenue of the Americas, New York, NY 10020, <http://www.mcgraw-hill.com/index.html>, 2000, xxxii, illustrations, 445 pp., \$75.00.

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