

CONGENITAL HEART DISEASE IN ADULTS

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FOREWORD

The senior author of this textbook, as a master clinician and educator, has few peers. He is unexcelled in his ability to communicate effectively the methods of patient examination, the interpretation of clinical data, and the thought processes involved in developing a differential diagnosis and a plan of management. These attributes have resulted in Dr. Perloff's being repeatedly selected for the highest teaching honors of both the American Heart Association and the American College of Cardiology. Furthermore, he has received outstanding teaching awards from every medical school and university on whose faculty he has served. Although Dr. Perloff is the "complete cardiologist," his mastery of subject material and his contributions are particularly focused on advancing the field concerned with care of the adult with congenital heart disease. His classic textbook, *The Clinical Recognition of Congenital Heart Disease*, is the preeminent sourcebook for serious students of this branch of cardiology. In *Congenital Heart Disease in Adults*, Dr. Perloff significantly extends his contributions by enhancing our understanding of congenital heart disease as it is seen in the older child and the adult.

As a result of remarkable progress in diagnosis, medical management, surgical techniques, and interventional catheterization, ever-increasing numbers of patients with congenital heart disease are entering adulthood. Moreover, increasing numbers of patients born with complex cardiac malformations are now reaching adulthood because newer techniques of repair are responsible for prolonged survival. This book provides a basic appreciation of the long-term consequences of congenital heart disease and therapies aimed at correction—an appreciation that is a prerequisite for structuring follow-up and management strategies in the adult. This book also provides a clear look at current and future approaches to the diagnosis and management of adults with congenital heart disease.

Congenital Heart Disease in Adults exemplifies the benefits of an effective and collegiate interaction among different disciplines and across jurisdictional medical school departmental boundaries. Dr. Perloff has created a model of splendid collaboration among pediatric and adult cardiology, cardiac surgery, nursing, radiology, hematology, obstetrics and gynecology, genetics, psychiatry, and social services that should serve as a standard for similar programs in this country and abroad. From the day he arrived at the UCLA School of Medicine, Dr. Perloff worked to form an effective and cohesive collaboration to enhance clinical care and to augment teaching and research in adult congenital heart disease—vital components of a center of excellence in this area. This book is unique insofar as it represents almost entirely a UCLA effort, with collaboration by consultants presently involved with the program or by graduates who have gone on to create similar programs in other institutions. The scope of the volume encompasses virtually all of the major aspects of diagnosis and management of the many disease states that afflict congenital heart disease patients surviving into

adult life and, thus, will serve as a reference book for internists, pediatricians, and general practitioners, as well as for pediatric and adult cardiologists. The sophistication of the material will make it useful to experts in the field, while its clarity of presentation will allow the neophyte to understand even the most complex subjects. Unlike most books with multiple contributors, Dr. Perloff has written himself or is a coauthor of 17 of the 20 chapters and has written the final version of each chapter. The text therefore reads like a single-authored book. The consistently lively style enhances readability and comprehensibility. For the many who are privileged to know Dr. Perloff and to enjoy his brilliant communicative style, reading this book will invoke memories of thoughtful and inspiring conversations with this exceptional and distinguished gentleman.

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PREFACE

The term "pediatrics" (Greek, *pais*, *païdo* meaning child and *iatria* meaning medical treatment) literally means "medical treatment of the child." Congenital (Latin *con* meaning together and *genitus* meaning birth) refers to patients who were "born together" (*congenitus*) with disease. Not surprisingly, medical treatment of patients born with malformations of the heart and circulation has necessarily and legitimately fallen within the province of pediatrics. However, natural survival beyond childhood has, as a rule, excited curiosity rather than committed interest and has not been a central concern of cardiologists responsible for the care of adults. Congenital heart diseases are not static anatomic defects but rather are dynamic disorders that originate in fetal life and change, often considerably, during postnatal development from the neonate to the infant, child, adolescent, and adult. The gaussian distribution of natural survival falls off rapidly with the passage of time, but the advent of cardiac surgery and cardiac catheterization 50 years ago anticipated that the distribution curve of survival would shift to the right. It was only a matter of time before one of the most successful rehabilitation efforts that medicine has witnessed would result in a new and thriving population of adults with congenital heart disease. By and large, results have outstripped preparation. It was not long ago that those who advocated a formalized study of congenital heart disease in adults were voices crying in the wilderness. But now the future is here. Congenital heart disease should be considered not only in terms of age of onset but also in terms of the age range that survival now permits. Adults with congenital heart disease represent a new category of specialized cardiovascular interest that requires cooperation among a number of medical cardiovascular and surgical disciplines and interaction across traditional departmental jurisdictions. This book seeks to address the wide scope of information currently encompassed by a new and evolving field. Twenty chapters in five sections include the historical background and special facilities, natural and postoperative (or postinterventional) survival patterns, medical considerations in unoperated and operated patients, surgical considerations (cardiac surgery, non-cardiac surgery, and cardiac catheterization as a therapeutic intervention), and postoperative residua and sequelae.

A prime objective of our efforts is to excite the interest of a broad range of health professionals—from the neophyte to the expert—in general medicine and pediatrics, general surgery and cardiac surgery, medical and pediatric cardiology, and general nursing and specialty nursing. The younger generation of health care professionals must ultimately assume responsibility for the task, and *Congenital Heart Disease in Adults* is designed to help them do so.

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Six pediatric cardiologists have materially contributed to the development of the UCLA Adult Congenital Heart Disease Center—Nigel K. Roberts, Mirka Zednikova, Gregory B. Wright, Alvin Chin, and Thomas V. Santuli. Particular thanks go to Samuel Kaplan, whose expertise, wisdom, and devotion to task single him out as a special colleague.

Our greatest debt is to our collaborators, who with few exceptions are, or were, UCLA colleagues, involved in the development and current activities of the Adult Congenital Heart Disease Center. Eighteen of the 20 chapters originated entirely at UCLA. Two chapters originated at the University of Iowa in collaboration with Dr. David J. Skorton, who, as a fellow, witnessed the beginning of the UCLA Center and who established a similar facility in Iowa. To all of these colleagues and collaborators, there are no limits to our thanks.

Dana St. John deserves much credit for her expertise and her patience in preparing the manuscript and in following it through the many drafts to its final stages. Robert D. Vinson of Merck, Sharp, & Dohme provided valuable assistance in the extensive literature search.

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SECTION

1

Pharmacokinetics

MARIANE McLAUGHLIN, PHARM.D.

BACKGROUND AND FACILITIES

Over the past 20 years the science of clinical pharmacokinetics has evolved from simple observation of how a drug is handled by the body to complex monitoring of drug concentration on an individual patient basis. The many advances made in this discipline apply to the relatively small number of pharmacologic agents for which a relationship between serum concentration and desired (or adverse) effect has been established. In general, a basic knowledge of pharmacokinetic principles has become a necessity to the clinician in order to effectively initiate and adjust the dosage regimen of patients receiving pharmacologic treatment. This chapter addresses pharmacokinetic principles, individual variability, and drug concentration monitoring. The pharmacokinetic information presented here is introductory, and the reader is referred to the pharmacokinetics texts in the References following this chapter for more detailed information. Specific pharmacologic agents are addressed in subsequent chapters.

Pharmacokinetics is defined as the time course of drug absorption, distribution, metabolism, and excretion. The effect of these functions on drug concentration is of major importance because an alteration in any one of them has the capacity to drastically change the concentration of active drug reaching its receptor site. In addition, the

dosage form itself can delay or enhance drug entry into the systemic circulation. A separate discipline known as biopharmaceutics is devoted to the study of product formulation and its effect on the release and absorption of the active drug. Yet another discipline, pharmacodynamics, is concerned with the study of biochemical and physiologic effects of drugs, or, in other words, their mechanism of action. Last, clinical pharmacokinetics is the science that relates the biopharmaceutics, pharmacokinetic, and pharmacodynamic information to patient care (Fig. 1-1).

LAODME

The acronym LAODME, which stands for liberation, absorption, distribution, metabolism, and excretion, is used to represent the pharmacokinetic processes that occur after administration of a medication. Liberation refers to the release of the active drug from the dosage form following oral administration. Absorption is defined as the transfer of the drug from the site of administration to the general circulation. Distribution refers to the movement of the drug from the circulation to various body fluids and tissues. Metabolism is defined as the biotransformation of the drug, usually to inactive, excretable forms. Excretion is the elimination of the

1

A BRIEF HISTORICAL PERSPECTIVE

Joseph K. Perloff

In any large series of geriatric necropsies . . . atrial septal defect is always well represented; where's the maladie de Roger? Assuming it does not provide immortality, it must either close spontaneously in middle life or have long since run its mortal course.¹

BACKGROUND

Congenital heart disease is, by definition, present at birth—*con* means “together,” *geni-* means “born”—but survival patterns vary widely. In 1888, Etienne-Louis Arthur Fallot wrote, “We have seen from our observations that cyanosis, especially in the adult, is the result of a small number of cardiac malformations well determined. One of these cardiac malformations is much more frequent than others. . . .”² Fallot was referring to the tetralogy that bears his name. In 1895, G. A. Gibson (best known for his description of the continuous murmur of patent ductus arteriosus) recognized Fallot’s tetralogy in a 64 year old woman.³ In the first half of the twentieth century, the untiring work of Maude Abbott, shown in Figure 1-1, culminated in her remarkable work, *Atlas of Congenital Heart Disease*, which was based on 1,000 pathology specimens that she personally studied.⁴ Not only was the atlas a landmark in the orderly classification of the anomalies, but it also provided invaluable information on natural survival patterns. The seminal contributions of Gross, Blalock, Taussig, and Crafoord soon followed, and the sense of despair that had surrounded congenital cardiac anomalies—



FIGURE 1-1. Maude E. Abbott (1869–1940), McGill University, Montreal. (With permission, Francis, W. W.: Maude Abbott. Bull. Hist. Med. 10: 305–308, 1941.)

those “hopeless futilities”—began to dissipate.

In 1939, Robert Gross, a pediatric surgeon in Boston (Fig. 1-2), ligated the patent ductus of a 7½ year old girl, “in the hope of preventing subsequent bacterial endocarditis and with the immediate purpose of reducing the work of the heart caused by the shunt between the aorta and the pulmonary artery. . . .”⁵ A few years later, Helen Brooke Taussig, a pediatric cardiologist in Baltimore (Fig. 1-3B),

FIGURE 1-4. Effect of the extent of absorption on the concentration versus time curve.



FIGURE 1-2. Robert E. Gross (1905-1988) Children's Hospital, Boston. (With permission, Nissen, R.: *Erlebtes Aus Der Thoraxchirurgie*. Georg Thieme Verlag, Stuttgart, 1955.)

conceived the idea of "creating" a patent ductus in cyanotic children suffering from deficient pulmonary blood flow. In 1945, Alfred Blalock, a vascular surgeon in Baltimore (Fig. 1-3A), sutured the end of the subclavian artery to the side of the pulmonary artery in a patient with Fallot's tetralogy, establishing the Blalock-Taussig anastomosis.⁶ "Heretofore there has been no satisfactory treatment for pulmonary stenosis and pulmonary atresia. A 'blue' baby with a malformed heart was considered beyond the reach of surgical aid."⁶ In the early 1940's, Clarence Crafoord of Stockholm (Fig. 1-4), while operating on certain patients with patent ductus arteriosus, "took the risk of placing clamp forceps on the aorta above and below the point of entry of the duct into this artery and of keeping them attached during the time necessary to divide the duct and suture the aorta."⁷ While performing the operation, Crafoord "began to wonder whether it might not also be possible to treat congenital coarctation of the aortic isthmus by surgical means."⁷ The postwar introduction of cardiac catheterization, for which Andre F. Cournand,

Dickenson W. Richards, and Werner Forssman were awarded the Nobel Prize in 1956, was a pivotal step forward. The development of extracorporeal circulation in the early to mid 1950's was destined to make virtually all congenital malformations of the heart accessible to the skills of cardiac surgeons. C. Walton Lillihei used controlled cross circulation for "direct-vision intracardiac correction of congenital anomalies," with the child's parent acting as the "oxygenator."⁸ Leland C. Clark's "oxygenation of blood by gas dispersion"⁹ was soon followed by John H. Gibbon's membrane oxygenator,¹⁰ which was adapted by John W. Kirklin to provide "accurate visualization of structures within the heart for a period sufficient to permit precise corrective measures."¹¹

MODERN CONSIDERATIONS

These historical discoveries introduced an era of one of the most successful rehabilitation programs that medicine has witnessed. Formidable technical resources are at our disposal, permitting remarkably precise anatomic and physiologic cardiac diagnoses and astonishing feats of reparative surgery. Survival patterns have been affected, often profoundly. In the last three decades, in the United States alone, well over a half million infants and children with significant congenital cardiac or vascular malformations have reached adulthood by virtue of medical or surgical treatment. Accordingly, congenital heart disease should be considered not only in terms of age at onset but also in terms of the age range that survival now permits—in essence, an uninterrupted continuum from fetal life to senescence. At present, long-term management remains concerned with natural survival but is increasingly concerned with the growing number of postoperative patients who continue to need surveillance. The quality of care provided by pediatric cardiologists from birth to maturity must be matched by continuing care of equal quality during adulthood.

Congenital heart disease in adults, which is the central topic of this book, is represented by natural survival and postoperative survival patterns that are shown in Table 1-1. Adults who have not been operated on now experience improved longevity and well-being owing to refinements in the medical management of hematologic disorders, renal function, urate metabolism, pulmonary physiology, suscepti-

FIGURE 1-3. A. Alfred Blalock (1899-1964), and B. Helen B. Taussig (1898-1986), the Johns Hopkins Hospital, Baltimore. (With permission, Cover of Science, Vol. 107. Am. Assoc. Advancement Science, April 16, 1948.)



bility to infective endocarditis, electrophysiologic abnormalities, pregnancy, and noncardiac surgery. Table 1-2 defines the types of surgical interventions currently used. Proper care of patients after operation assumes knowledge of the preoperative congenital heart dis-

Table 1-1. SURVIVAL PATTERNS OF ADULTS WITH CONGENITAL HEART DISEASE

Natural Adult Survival

- Malformations that do not necessitate an operation
- Malformations that remain amenable to operation
- Malformations that are inoperable except for organ transplantation

Postoperative Adult Survival

- Natural adult survival enhanced by operation
- Adult survival related chiefly or solely to operation

ease, the nature and effects of the surgical intervention, and the presence, type, and extent of postoperative residua and sequelae. The ideal of complete cure is rarely achieved. Accordingly, operations necessarily leave behind a broad range of residua and sequelae that require prolonged, if not indefinite, medical attention.

Congenital heart disease in adults has emerged as a special area of cardiologic interest.^{12, 13} Uninterrupted, long-term continuity



FIGURE 1-4. Clarence Crafoord (1899-1984), Karolinska Institute, Stockholm. (With permission, Nissen, R.: *Erlebtes Aus Der Thoraxchirurgie*. Georg Thieme Verlag, Stuttgart, 1955.)

Table 1-2. TYPES OF SURGERY FOR CONGENITAL HEART DISEASE

Surgery Type	Characteristics
Curative	No postoperative residua, sequelae, or complications
Reparative	Anatomic repair or reconstruction with obligatory postoperative residua or sequelae
Palliative	Neither repairs nor reconstructs the basic anomaly
Reoperative	Late reoperation after reparative or palliative surgery
Organ transplantation	Heart, heart-lung, isolated lung