The Natural and Unnatural History of Congenital Heart Disease
This book is dedicated to my wife Kathy and my children Anna and Daniel who supported me during this long gestation.
The Natural and Unnatural History of Congenital Heart Disease

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Daily, cardiologists and surgeons make management decisions about children and adults with congenital heart disease. Questions arise such as, what is the course of this child's condition without treatment? Among options which has a better outcome, an interventional procedure or an operation? What are the long-term consequences of a particular treatment? Often our answers are based on our own experience, opinions of colleagues or from selective or limited reading of the literature.

Julien Hoffman’s monumental work, “The Natural and Unnatural History of Congenital Heart Disease” provides an invaluable resource to guide decisions about the treatment of cardiac malformations based on data from the literature. In its more than 50 chapters, each devoted to an individual cardiac anomaly, a comprehensive compilation and interpretation of data about the natural course and the short and long-term course following treatment is presented. The chapters are meticulously and extensively referenced; for instance, the chapter about tetralogy of Fallot has nearly 500 references alone.

The book is a milestone in pediatric cardiology reflecting the long experience of Julien Hoffman as a cardiologist, author and investigator. It is tempered by his wisdom. He compiled the relevant literature, interpreted it through text, tables and extensive use of graphs and rendered it useful to those of us who care for patients. The ultimate beneficiary of this effort will be the individuals with congenital heart disease requiring appropriate decisions about their care.

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There are many unsolved problems about how to treat a congenital heart disease. Which is better for treating a coarctation of the aorta – surgery or balloon angioplasty? Should an asymptomatic 65-year-old patient with a mild tetralogy of Fallot have a complete correction? Does a child with a small, silent patent ductus arteriosus need to have it closed? Should a patient with congenitally corrected transposition of the great arteries without a ventricular septal defect or outflow tract obstruction have an arterial switch, and if so, when should this be done? These are among the many unsolved problems, and the answers to these and similar questions will not be known for many years. Nevertheless, despite the lack of definitive information, cardiologists daily have to make decisions about treating individual patients.

The objective of this book is to evaluate the natural history of congenital heart lesions as a background to finding out if and to what extent treatment has improved outcomes. To do this, the early literature has been searched for information about what happened to these patients in the days before surgical treatment became available. This information can then be compared with the outcomes of surgical and, more recently, interventional catheter-based treatment, and different forms of treatment can be compared with each other. A lot of data about natural history are contained in individual case reports, and sometimes assembling all these reports gives a picture that belies conventional wisdom about the effects of the lesion. While gathering data for this book, I have realized that many statements in current texts about the natural history of a particular lesion are either incorrect or at least biased towards a subset of the lesion. Correcting these incorrect impressions could have some influence on future treatment of patients who do not belong to that subset. For example, texts frequently cite a standard natural history curve derived for patent ductus arteriosus, based on reasonably extensive autopsy data, and this shows that the median survival time without treatment is about 30 years. Reading the original articles confirms this figure, but makes clear that all of these were very large ductuses that in reality are in the minority. Most patent ductuses are small, and the natural history of large ductuses gives us little useful information on which to base therapeutic decisions.

The literature about any congenital heart lesion is vast, and there are many publications that are given as references that appeared in journals that were not readily accessible. Unless these appeared to be essential, I have ignored them and have not attempted to list everything that is in print. On the other hand, I have tried to give a comprehensive bibliography for each lesion. Most of the figures are presented as survival curves. Patient survival is compared with the survival curve for the whole population. Although there are differences in population survival curves at different eras and in different countries (see chapter 1), I have chosen one standard curve for the United States taken from Anderson [1] (#24) because the small differences between population survival curves pale in comparison to the patient survival curves. These normal survival curves are shown as thick black lines at the top of each figure.

For each lesion discussed an introduction defines the lesion, and gives some general information about its frequency, familial or syndromic associations, and associated congenital heart lesions because these have an effect on its outcome. This section is followed by sections on pathological anatomy and physiology that determine outcomes. I have ignored entirely clinical and laboratory diagnosis, but where relevant have included the initial clinical presentation that may at times define important subgroups. Then what is known of the natural history is presented, mainly in terms of survival but also at times relative to symptoms and various abnormal occurrences such as arrhythmias. After this section, the results of treatment are presented, both as survival and also as event-free survival, that is, survival free of reoperation, cardiac failure, arrhythmias, and other late complications that are often seen. Where applicable, the results of surgery are compared with the results of interventional catheter-based treatment. I have included all the major and not so common congenital cardiovascular lesions that occur, but have omitted certain lesions. A few rarities such as connection of a left superior vena cava to the left atrium have been omitted because of lack of data and because treatment would be expected to be relatively simple and effective. What is more important is that there are many patients who have unusual combinations of
lesions, but no one combination occurs with enough frequency to provide useful data.

The semanticists pointed out many years ago that to give something a name is to risk having it thought to be a single homogeneous entity. This error applies to congenital heart diseases as well. Consider, for example, the entity known as transposition of the great arteries. It is possible to present the survival of patients with this lesion who have had an arterial switch, and anyone examining the curves can come away with a prediction of how likely the next patient who has this operation is to survive for 10 years. In reality, transposition of the great arteries is a collection of lesions that share certain common features. A simple transposition of the great arteries with an intact ventricular septum is the commonest form of this anomaly, but has a dozen or more coronary arterial patterns, some of which influence outcome. Then another subset has one or more ventricular septal defects, each of which has the coronary arterial variations mentioned. Some of these patients have had prior palliative surgery. In some there are minor abnormalities of valves or outflow tracts, of ventricular volume and mass, of aortic size; some will be small for gestational age or premature. In fact, there are so many possible variations that no two patients are exactly the same. In reality, the sample size for a given combination has an N of 1! Occasionally some of these variations are distinguished in the survival curves, but it is not possible to allow for them all. Therefore any cardiologist has to interpret the survival curves with care, and must realize that the more closely a patient fits the average the more accurate the prediction given by the survival curve is. Conversely, for a patient with an unusual combination of features the average survival curve may be grossly misleading. This problem is compounded by the fact that no two surgeons do an operation, especially a complex operation, in exactly the same way. Moreover, even a given surgeon will alter the operation to deal with anatomic variations that distinguish one patient from another.

Notwithstanding these criticisms, it is possible to derive information from survival curves as long as one realizes that the results apply to an average patient, not any specific one. In some figures, the data from several series that are plotted are superimposed to the extent that it may be difficult to distinguish the symbols from one set of data from another. This has little importance because they are all almost all the same. If, on the other hand, the curves are widely divergent from each other, then each series can be readily identified and examined to see why it differs from the others.

The definition of congenital heart disease is not cut and dried. Most cardiologists use the definition of Mitchell et al. [2]: congenital heart disease is “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance.” This definition excludes abnormalities of the great veins, such as persistent left superior cava (even though this might be important during surgery). I have adopted this usage, and omitted pediatric cardiological diseases such as congenitally determined arrhythmias, dilated and hypertrophic cardiomyopathies, and Marfan syndrome.

My hope is that the information put forth in this book will help cardiologists and cardiac surgeons understand what is likely to happen to patients with or without treatment, and which forms of treatment currently in use provide the best outcomes to date. None of our treatments is perfect, and we look forward to continual improvements in the outcomes.

I have received considerable help from several people to whom I owe a great debt of gratitude. Dr James Moller carefully read, criticized and improved each chapter by many helpful suggestions. Dr Phillip Moore helped to provide insights into interventional catheterization techniques and results. Dr Kenji Suda obtained and translated for me some Japanese publications that were unavailable here. Important unpublished information was provided by Dr Don Hagler, Ms Judith Lenoch, Dr Brian McCrindle, Dr R. Garcia Rinaldi, Dr Colin Phoon, and Dr Anthony Azakie. Drs Gary Grunkmeier and Eugene Blackstone shared with me their thoughts about competing risks analysis.

The books and publications that I have consulted are numerous, but two need special mention. The classic textbook, Cardiac Surgery by Kirklin and Barratt-Boyes [3], was invaluable in terms of organization, history, and references and, of course, details of the surgical techniques and their carefully analyzed outcomes. The other invaluable book was the last great contribution of the late Robert Freedom, written with S-J Yoo, H Mikailian, and W. Williams, The Natural and Modified History of Congenital Heart Disease [4]. In comparing that book with mine, their book has more on presentation and diagnosis, less on the details of the natural history, more about some of the rarities that I do not discuss, and a different approach to the effects of treatment. They have analyzed the results of several major surgical and interventional treatment series in depth, with careful discussions of the specific outcomes of each series. I have provided more comprehensive but more general information, the merit of which is to give a broad picture that is to some extent independent of the individual techniques used. I regard the two books as complementing each other rather than being in competition.

Almost everyone working on natural history of congenital heart disease owes an enormous debt to the late Maurice Campbell for his immense contributions to the field.

Julien I.E. Hoffman

1 Introduction
1 Practical and Theoretical Considerations

**Considerations: natural history**

Knowing the natural history of any disease, that is, what happens to people with that disease without treatment, is a prerequisite for knowing whether, when, and how to treat it. For many diseases, the natural history is well known, but this is not true for congenital heart disease.

To appreciate the problems, imagine designing a study of the natural history of a congenital heart lesion. One way would be to diagnose within a given year with certainty every child with that particular congenital heart disease immediately after birth. The diagnosis includes the basic lesion, any relevant subtypes, and an estimate of severity. Then each subject in the cohort is followed without treatment until death (longitudinal or cohort study).

Now consider the barriers to such a study. In the USA there are about 40,000 children born each year with some form of congenital heart disease. When broken down into subtypes, however, the numbers with any subtype may be small enough that births will need to be monitored for several years to provide consistent data. Second, the duration of follow-up might have to be very long. For example, the oldest recorded patient with an atrial septal defect lived to be 96 years old. Finally, accurate diagnosis by cardiac catheterization became available only in the 1950s, and even later for infants. By that time, surgical treatment of major forms of congenital heart disease was available, so that it was impossible to follow for life untreated patients who had been diagnosed with certainty. In addition, many forms of congenital heart disease that cause early death may not be diagnosed without an autopsy examination [1,2] and autopsies are not always done. Apart from these problems, patients followed for many years without cardiac surgery cannot be regarded as having no changes in nonsurgical care during their lifetime.

The longitudinal method implies that the outcomes would be the same for patients born in any year, a process known as stationarity, and this is unlikely to be true because of nonspecific changes in medical therapy. Improved treatment of congestive heart failure, infective endocarditis, and pneumonia has altered the natural history. Nevertheless, improved survival from these medical treatments was probably modest. Digitalis and diuretics were used early in the 20th century, but prolonged life by no more than a few years. The only change that made a difference was antibiotic treatment for pneumonia, infective endocarditis, and tuberculosis, all of which previously accounted for many deaths in these patients. From that time until the extensive application of surgery to this population, there were no substantial improvements in medical treatment. Therefore some degree of stationarity exists, and differences from early in the 20th century up to the advent of cardiac surgery probably had little effect on the natural history of congenital heart lesions.

**Longitudinal and cross-sectional analysis**

These problems do not mean the natural history of congenital heart disease was not studied before the 1950s. Clinical diagnoses of patent ductus arteriosus, ventricular septal defect, pulmonic and aortic stenosis, coarctation of the aorta, and tetralogy of Fallot were made, although seldom in neonates. However, modifiers such as size of shunt or pressure gradients were often not available. There is one significant exception to these criticisms. In Bohemia (at that time in Czechoslovakia), there was excellent diagnostic cardiology but virtually no cardiac surgery until recently. Samánek et al. [3,4] took the opportunity to obtain the natural history of well-defined forms of congenital heart disease. The only problems with those studies were that the total numbers in each type of congenital heart disease were quite small, and prolonged follow-up until death of all the patients with a given lesion was not possible.

A second approach would be to examine a large series of untreated subjects with a particular form of congenital heart disease at a given time (cross-sectional study). For example, if 50% of untreated subjects with tetralogy of Fallot were over 10 years old,
then the cumulative mortality would be 50% by 10 years. (A crucial assumption is that the group of patients is representative of all those patients, and this will be discussed below.) This cross-sectional approach also requires stationarity; that is, a group of children born in any year would have to have had the same natural history as a similar group born in any other year. Once again, the requirements for accurate diagnosis and the absence of any treatment cannot be completely fulfilled. One way of dealing with the need for precise clinical diagnosis would be to examine data obtained in a series of autopsies of subjects who died for reasons other than surgical treatment of their disease. In the days prior to effective surgical treatment, precise diagnosis could be and was made by autopsy, and selection based on therapeutic possibilities was not an issue. It is, however, not always possible to determine if autopsies were done in unselected patients, or if knowledge that an institution was interested in certain types of congenital heart disease resulted in selection bias. Nevertheless, pathologists and cardiologists shared a growing interest in congenital heart diseases after 1940, and this led to large numbers of autopsies in patients with these diseases.

The equivalence of longitudinal and cross-sectional data (given stationarity) may not be obvious. To show their equivalence, consider a congenital anomaly in which all the patients die within five decades (Fig. 1.1).

Starting with the first cohort, there are 100 people born with this anomaly. Fourteen of them die before the end of the first decade, 26 die before 20 years of age, 33 die in the third decade, 20 in the fourth decade, and the remaining 7 in the fifth decade (top panel, shaded columns); there are no survivors over 50 years of age. One decade later another cohort is followed (second panel from top) and, assuming stationarity, follows the same course. This pattern is followed in successive decades (next three panels). Therefore, no matter which cohort we follow, 14% die under 10 years of age, 26% between 11 and 20 years of age, and so on. Any combination of first, second, third, fourth and fifth decades will give the same data. One such combination is shown in the cross-sectional data marked by the arrow and the vertical shaded columns. There are 14 dead under 10 years of age, 26 dying between 11 and 20 years of age, 33 dying between 21 and 30 years of age, and so on. If there is stationarity, then the numbers dying in each decade will be the same for longitudinal as for cross-sectional studies.

The same data plotted as survival curves are shown in Fig. 1.2. This analysis assumes that we have data on the ages at death. However, we can use the ages at which patients enter an institution to obtain similar information; certain caveats are discussed below. If the numbers of patients presenting to hospital or clinic are, by decade, 14, 26, 33, 20, and 7, then the cumulative numbers are 14 by 10 years of age, 40 by 20 years, 73 by 30 years, 93 by 40 years, and 100 by 50 years. If 14% of all the patients admitted are under 10 years of age, then there must be 86% of patients who are alive after 10 years of age. If 40% of patients have appeared by 20 years of age, then there must be 60% who are alive after 20 years of age, and so on. Calculating the numbers appearing at each subsequent age yields the same survival curve as shown in Fig. 1.2. A demonstration of the equivalence of age at death in autopsy data and age of appearance in a clinical series is shown in Fig. 1.3.

Natural history is least accurate for those with cyanotic congenital heart disease. There are innumerable forms of these, each variant with its own natural history, but because numbers are small, the mixture of variants differs from series to series. For example, in pulmonary atresia with an intact ventricular septum outcome is determined by variations in the size of the ductus arteriosus, whether there are right ventricular to coronary artery sinusoidal connections, whether the main coronary arteries are connected to the aorta, the size of the hypoplastic right ventricle, and whether or not the tricuspid valve is competent. These variations are impossible to diagnose without modern diagnostic techniques or autopsy examination. Even if diagnosed, the resultant subgroups may be too small to provide accurate predictive information.

For the cross-sectional method to give an accurate estimation of the natural history, the patients in any series must represent all the patients with that particular lesion. This requirement is
fulfilled if all the patients with that lesion in a region are diagnosed, or if they are a random sample of those patients. In general, patients with symptoms are likely to come to medical attention, but whether those who are asymptomatic are randomly selected is uncertain. Published series include many patients without symptoms, but there is no way of knowing what proportion they form of all such patients. If patients have prominent physical findings, such as very loud murmurs or cyanosis, they are very likely to be referred to a cardiologist. If the findings are subtle, however, diagnosis may be delayed or possibly never made at all. We know that perhaps as many as 50% of patients with atrial septal defects are not diagnosed until they are adults [7,8]. This does not matter if they are eventually diagnosed, because they will ultimately be included in the natural history statistics. If, however, some are never diagnosed, then the deduced natural history will appear worse than it really is.

Even the cross-sectional method breaks down as medical science advances. When cardiac surgery became safe for infants, the tendency was for all infants detected with a given lesion, for example, tetralogy of Fallot, to be corrected. This precludes developing the natural history of this lesion, and natural history must be determined from studies done years ago when early surgery was not generally available. Similarly extensive clinical networks in many major regions detect almost all forms of congenital heart disease in the first year after birth [9,10] and the opportunity to determine the natural history today has become much more difficult if not impossible.

Survival curves

Special care must be taken when interpreting the age distribution of a series as indicating the survival curves when other features of the natural history suggest considerable longevity. Consider two congenital lesions in which prolonged survival is common: bicuspid nonstenotic aortic valve, and coronary arterial fistula. Patients with bicuspid aortic valves fare well, with few deaths under 40 years of age and a relatively steep decline after that as the valves deteriorate. This lesion may not be diagnosed until later life because the abnormal physical findings may be subtle. Patients with a congenital coronary fistula also have few early deaths, most after 40 years of age, so that the survival curve resembles that of the bicuspid valve. The coronary fistula however has a prominent and characteristic continuous murmur that leads to early referral.
Consequently, the curve showing the ages at which the coronary fistulae are detected differs markedly from the curve of survival versus age (Fig. 1.4). If the curve relating detection to age were interpreted as the survival curve, then an incorrect assessment of a high early mortality would be made.

**Presentation of data**

If the outcome of interest is survival rather than symptoms, then survival curves for a particular type of congenital heart disease can be plotted against the reference survival for the whole population [11] (Fig. 1.5).

This figure shows survival curves for the whole population, and generalized characteristic survival curves for those with acyanotic and cyanotic lesions. Generally, those dying young have the more severe disease than those dying late; however, many old people with acyanotic congenital heart disease have lesions that are not minimal. The consequences of an abnormal communication or obstruction depend not only on the severity of the lesion but also on the ability of the heart to deal with it.

The normal survival curve for the whole population is not fixed. It differs slightly for different years (Fig. 1.6, left panel) and for each gender (right panel).

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**Figure 1.4** Data for coronary arterial fistulae (chapter 12) to show the difference between the age at clinical presentation (two left-hand curves) and age at occurrence of symptoms or death (two right-hand curves). PM, autopsy data.

**Figure 1.5** Idealized survival curves.

**Figure 1.6** Population survival curves for three different time periods [11–13] (left panel) and the two genders [11] (right panel).
Theoretically the appropriate curves should be used for comparison with clinical outcomes, although for most publications results for men and women are not separated. For assessing natural history of congenital heart disease, however, clinical data are not accurate enough to warrant correction for these variations.

There are also differences between countries, and differences related to associated factors such as smoking. When comparing large groups with these normal data we expect these differences to be similar in control and treated populations, but if the treated population is small it may well have a different mix of genders or other factors that affect the comparison.

Survival curves are easy to plot for survival from birth. When, however, survival in a group of patients who are, for example, 40 years old is assessed, allowance must be made for the fact that these are the survivors of a larger group in which the younger members have died. This almost always means that the older subjects had less severe disease, and what happened to those with more severe disease has little bearing on the survival of these older subjects. On the other hand, the older subjects might develop myocardial or coronary arterial disease, or other noncardiac diseases that influence outcome. These older subjects therefore require their own survival curves.

There is no entirely satisfactory way of depicting (and analyzing) the outcome of surgery done at different ages. This can be illustrated in Fig. 1.7(a–d) with data taken Clarkson et al. [14] of survival after surgery for coarctation of the aorta performed at average ages of 11, 29, and 48 years.

Figure 1.7(a) shows the survival curves for all people (normal curve, thick solid line), for those with untreated coarctation of the aorta (natural history curve, solid thin line, based on pooled autopsy data), and for those operated on at three different age groups. The surgical outcomes are shown as a percent of those surviving surgery and followed for up to 20 years, and all these curves start at 100% from the origin. Survival rate is best for the youngest and worst for the oldest group, but the oldest operative group apparently does worse than those without treatment. The x-axis in fact represents two scales: one in absolute years applies to the normal and natural history curves, and the second, also in years, refers to the time after surgery for each group. In addition, although it is reasonable that older patients have a less favorable survival, the relative disadvantage of the oldest group is difficult to quantify. To allow for the difference in starting ages, we can move the origins of each surgical outcome curve to the mean age at the time of surgery (Fig. 1.7b). This puts each curve in the appropriate age range, so that the x-axis reads both absolute age and the time after surgery. However, some of the outcome curves start above the normal curve, and this is corrected simply by moving each outcome curve down to start at the appropriate age on the normal survival curve (Fig. 1.7c), reducing the 100% value to the appropriate percentage at that age on the normal survival curve, and changing the remaining postoperative survival percentages by a similar proportion. In each age group, the survival after surgery is not as good as for normal people. On the other hand, whereas in (b) it was possible to interpret the percentages surviving at different times after surgery, in (c) this cannot be done exactly without recalculating the data because now the curves do not start at 100%. Furthermore, the degree of departure from the normal curve is difficult to quantify. Finally, because patients would be expected to have less good survival than the normal population, it is difficult to interpret the improvement (if any) of the surgical outcome over the natural history. To deal with this last point, we can start each surgical outcome curve at the appropriate point on the natural history curve (Fig. 1.7d). In doing this, however, we must make allowance for the fact that a group of, say, 30-year-old people with coarctation of the aorta does not represent all with coarctation. At best, it represents all 30-year-old people with coarctation. For this reason, 100% survival of these operated patients has to be adjusted to the percentage of untreated coarctation patients who survive 30 years of age, about 55% (arrow A, left dashed line). If their 23 year survival after surgery is 70%, then this is equivalent to 70% × 0.55 = 38.5% (arrow B, right dashed line). (A specific example of this adjustment is shown in Fig. 1.3 where the raw data reported by Connolly et al. [6] for patients over 20 years of age are corrected to the percentage surviving to 20 years of age in the pooled autopsy series.)

Figure 1.7(d) shows that, in terms of survival, surgery improves on the natural history for the two younger groups, but is little different from it in the oldest group. The natural history curve at older ages, however, is based on small numbers, and is inaccurate. Furthermore, even if survival is not improved, there may well be relief of symptoms and improvement in the quality of life that cannot be judged from this graph.

The curves shown in Figs 1.7(c) and 1.7(d) differ only by a scale factor and the reference curve to which they are related. To change a survival curve related to the population survival curve (Fig. 1.7c) to its counterpart related to the survival curve for that lesion (Fig. 1.7d), multiply each value on a given curve by the factor: [percent survival of natural history population at the age at the time of surgery/percent survival of normal population at that age]. For the reverse transition, the factor is the inverse.

Few patients with cyanotic heart disease reach adult life without treatment (Fig. 1.5), so that the correction shown in Fig. 1.7(d) for older age groups is not possible. The best that we can do is to display the data as shown in Fig. 1.7(c). If the older age group has both treated and untreated subjects, however, then these can be compared directly. Nevertheless, such a comparison must be done with caution because of possible differences in age distributions and means. To give an example, consider a group of adults of whom 40 are aged 20 years, 20 are aged 40 years, and 10 are aged 60 years for a mean age of 31.6 years. From the pooled autopsy data in Fig. 1.5, the 20-year survival of each group would be respectively from 62% to 31%, from 31% to 10%, and from 10% to 1.4%, yet for the pooled group with mean age 31.6 years the expected survival would be from 41% to 28%. This pooled estimate underestimates survival of the youngest group and overestimates that of the oldest group and departs from the actual natural history curve. Furthermore, the pooled estimate will vary with the distribution of ages in the group.
Iacovino [15] made an important point about the effect of a wide distribution of ages at the time of surgery. If, for example, the ages at the time of surgery ranged from 48 to 52 years, with a mean of 50 years, then the group is homogeneous for age and age-related illnesses. A standard survival analysis gives the annual survival. If, on the other hand, ages ranged from 30 to 70 years, also with a mean of 50 years, then the standard survival analysis is misleading. During a calendar year, more of the older than the younger subjects in the group would die, causing the mean age of the survivors to be less than a year older than the group age was at surgery. Therefore each year the group behaves more and more like a younger group, with obvious survival advantages.

A specific example of the artifact due to a wide age distribution may be taken from comparing survival of medically and surgically treated adults with a patent ductus arteriosus reported by Fisher et al. [16] and illustrated in Fig. 1.8.

Forty-five subjects aged 20 to 81 years (mean age 43 years) did not have ductus closure, and 72 subjects aged 18 to 68 years (mean age 32 years) had surgical closure of the ductus; the study was not randomized. Comparison of the 20- to 35-year follow-up...
of these two groups when both were plotted starting at 100% showed a clear advantage for surgical treatment (Fig. 1.8, upper left panel). However, we expect the survival to be worse for a group with a mean age of 43 years than a mean age of 32 years even in the absence of differences in treatment, as suggested by the curves in Fig. 1.8, right panel. If we correct each group by allowing for the normal survival at the mean age of each group, as shown in Fig. 1.8 (upper right panel), then the disparity in survival between the normal population and both ductus groups is less marked, although the surgical group still appears better. This new figure shows essentially the raw data shifted to the right to start at the appropriate mean ages. If, however, the data are plotted relative to the survival curve obtained from pooled autopsy data (Fig. 1.8, lower panel), there is initially no advantage for the medically treated group, but after about 7 years their survival parallels that of the surgical group and both improve on the natural history. Many unoperated patients had pulmonary vascular disease and would be expected to have reduced survival, but others did quite well. These alternative ways of displaying data emphasize the care needed in interpreting survival data in older subjects.

In a controlled clinical trial of medical versus surgical treatment of atrial septal defect in adults, Attie et al. [17] divided outcomes into age groups (Fig. 1.9). In both the medical and surgical groups the survival was worse for the older patients. In fact, comparing the younger medical with the older surgical group, the medical group comes out with slightly better survival. It was only by comparing groups with similar ages that they were able to show a better outcome over the next 10 years from surgical treatment.

**Ascertainment bias**

For a cross-sectional study to provide an accurate natural history survival curve, not only must there be stationarity, but the numbers of subjects of different ages in the study must be proportional to their numbers in the population. Random departures...
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from proportionality may distort the curves if the total number of subjects is small. One source of bias is inclusion of only the more severe examples of a particular lesion in an autopsy or clinical series. For example, surgery for pulmonic stenosis was done originally only on those thought to have marked stenosis, so that a cross-sectional survey of these patients yielded age distribution data that excluded milder examples and lead to an unduly pessimistic outlook for survival. Then there is bias because certain age groups are underrepresented. In some studies only adults are included; allowance must be made for the missing children, and this can be done by assuming that the starting age for the series of older patients has less than 100% survival (see Fig. 1.7 and associated text). In other studies the series begins with birth but older age groups are not fully represented. Most subjects with congenital heart disease were usually seen by pediatric cardiologists in a children’s hospital or in a children’s section of a general hospital, and there may be disproportionately few older subjects reported from these institutions. To evaluate the effect of this deficit, I altered a typical natural history curve for patent ductus arteriosus reported by Campbell [18] by reducing the numbers of subjects over 20 years of age to 10% or 50% of their actual numbers. The results are shown in Fig. 1.10 (left panel).

The left panel shows survival curves for the normal population, for patent ductus arteriosus reported by Campbell [18] (thin solid line), and for two data sets derived from Campbell: in one, the subjects over 20 years old are reduced by 50%, and in the other they are reduced by 90%. The right panel shows an example in which the truncated series of patients with congenitally corrected transposition of the great arteries reported by Friedman and Nadas [19] from a Children’s Hospital is compared with a complete series from a general hospital reported by Yeh et al. [5]. Underreporting of older patients is evident from the data from a children’s hospital, but almost certainly a general hospital will

Figure 1.9 Surgical vs medical follow-up of older patients with atrial septal defects, redrawn from data of Attie et al. [17].

Figure 1.10 Ascertainment bias.
have missed some of the infants who were referred to children’s hospitals.

The effect of undercounting older subjects makes the early portions of the survival curves much steeper. When the deficit of older subjects is extreme, the survival curve resembles that for cyanotic heart disease (Fig. 1.51).

There are other types of bias. There has always been considerable interest in reporting examples of congenital heart disease in older adults, but not for younger patients unless some specific reason leads them to be included. For example, an 80-year-old patient with a secundum atrial septal defect is a rarity and worthy of report, but there would be no interest in reporting a 5-year-old with an atrial septal defect. On the other hand, if a surgical procedure previously done only in older children is modified for neonates, there will for a while be an excessive number of reports of this new application.

A good example of these problems can be found in assessing the natural history of an aortopulmonary window. In one report, pathology collections in four institutions in London, Leeds, Liverpool, and Pittsburgh were examined for autopsies done on subjects with this anomaly; the results are shown in the survival curve in Fig. 10.1, along with a smaller series reported from Gainesville, Florida [20]. A second survival curve based on all autopsies reported in the literature by Neufeld et al. up to the time of publication in 1962 [21] is also shown, and shows what appears to be a much better survival than the first.

There may be several reasons for this. The report by Neufeld et al. was drawn from the worldwide literature and therefore represents a referral population of a billion or more, whereas the report from institutions has a referral population of about 25 million. It is more likely that the larger population will contain more outliers, and this with the tendency to undercount young children results in what appears to be a much better survival. In addition, the four institutions used by Ho et al. and the one from Florida had a long-time interest in congenital heart lesions in children, whereas many of the reports in the study by Neufeld et al. came from general hospitals and adult medical services. It is difficult to avoid thinking that the survival curves based on mixed literature surveys may overestimate the true survival. We expect that the ages at admission for surgery would reflect the natural history better, and this is supported by the data shown in Fig. 10.2.

**Cause of death**

Most deaths of patients with congenital heart disease who die under 40 years of age are due to the heart disease, except in the immediate postnatal period; in the whole population, the death rate from all causes is very low under 40 years of age. After 40 years of age, however, an increasing proportion of deaths is due to common diseases such as cancer, coronary arterial disease, hypertension, diabetes mellitus, strokes, and renal disease to which everyone is prone. Therefore when evaluating the effects of surgery in older subjects with congenital heart disease, we must separate deaths related to heart disease or its repair from nonspecific causes of death. These associated diseases also affect decisions about treatment. For example, a 50-year-old patient with a moderate sized atrial septal defect might have no symptoms until hypertension and coronary arterial disease add to the burden on the heart. Whether closing the defect will have the same effect in this subject as in one without the associated diseases is difficult to predict from existing natural history data.

**Theoretical and practical considerations: unnatural history**

Although controlled clinical trials are regarded as the ideal, observational trials have some advantages. Observational data are cheaper to obtain, and often represent the spectrum of disease better than does the more specific clinical trial. They are likely also to include a longer time of observation. However, outcomes may well vary depending on the severity of the problem that the subject had before treatment. Most neonates with simple complete transposition of the great arteries can be considered to be seriously affected to a similar degree, and group outcomes give much information. On the other hand, the outcome for subjects with atrial septal defects varies with age at operation, defect size, presence of congestive heart failure, severe mitral or tricuspid valve regurgitation, atrial arrhythmias, and degree of pulmonary hypertension. It may be even more difficult to compare surgical results for the repair of complex anomalies that have different combinations of individual lesions, for example, in congenitally corrected transposition of the great arteries a patient may have a ventricular septal defect, outflow tract stenosis of the pulmonary ventricle, tricuspid regurgitation, right ventricular dysfunction, or any combination of these, not to mention the possibility of having additional lesions such as a straddling tricuspid valve or coarctation of the aorta. Because any individual surgical series is not likely to be very large, the mix of lesions is not likely to be the same for each series.

An example of how to deal with this problem appears in a study of treatment of critical aortic stenosis in neonates [22]. Ideally, to compare the outcomes of surgical versus balloon valvotomy in infants with critical aortic stenosis, we should design a controlled clinical trial with patients randomized to one or the other group. Because variables such as coarctation of the aorta, mitral stenosis, endocardial fibroelastosis, and ventricular size influence outcome, we might stratify the randomization to include equal numbers of each of these in the two groups. In practice, most studies are performed by observation without any assurance that patients were allocated at random to each group. Different treatments might depend on physician preference, the period in which treatment was done, which hospital was used, and so on. Therefore if we find a difference in outcomes for the two methods of treatment, how can we be sure that it was the treatment that caused the difference rather than the differences in numbers and types of complicating lesions? Comparing individual subgroups might be attempted, but numbers will be small
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and there is still no assurance that other unmatched variables are unimportant. In fact, even if the database is large, there is still no certainty in drawing conclusions from the raw data [23,24]. One way of handling this problem is to use the Cox proportional hazards regression model [25]. Others are to use propensity analysis [26] or bootstrap methods [27,28].

Determining survival after surgery could in theory be done longitudinally. A large homogeneous group of patients, for example, with a stenotic aortic valve replaced are followed until all are dead. Percent survival versus time can be determined, and two or more groups can be compared; for example, homograft versus mechanical valves. The difficulty with this approach, just as for natural history, is that the group(s) would have to be followed for very many years. In addition, it might not be possible to find huge numbers of patients operated on in a given year, and results of operations done over 5–20 years might have to be merged. These problems can be handled by constructing actuarial survival curves, a blend of longitudinal and cross-sectional methods, that were well known to statisticians involved in constructing life tables or determining time-to-failure of manufactured items. The methods were introduced into medical research by Kaplan and Meier [29] and were popularized in surgery by Anderson et al. [30]. Both actuarial and Kaplan-Meier methods are similar; the actuarial method examines the cohort at fixed time intervals (usually one year), and the Kaplan-Meier method recalculates the outcome each time a patient dies, so that the survival curve has irregular intervals. These survival curves are very useful, but have weaknesses. When patients whose operations were done at vastly different times form a single database, the analysis holds only if there is stationarity. In surgery, however, methods change with time, usually for the better. Therefore patients who have survived for, say, 25 years, are a fraction of all patients operated on by those older techniques, and it is likely that the 25-year survival fraction of those operated on today by current techniques would be larger.

There is another aspect to evaluating results of a series of data collected over many years. In many forms of congenital heart disease there has been, with time, a reduction in early postoperative mortality, but survival for those leaving hospital has not changed. If the data from these different period are combined, an artifact might not have been included in earlier times. I have tried to deal with this issue by plotting the early mortality against the year the series began (start year), the year it ended (end year), or the average (mid-year) (Fig. 1.12).

In this example, the early mortality of pulmonary artery banding is plotted against the year the series began, the year it ended, and their average. For both sets of lesions mortality decreases with time, and mortality is less for the simple than more complex lesions. The pattern is similar for all three depictions, so that I have chosen the mid-year for all future figures of this type.

Event-free survival

When assessing the results of treatment it is convenient to consider two sets of outcomes. The first is survival, once the important outcome, but less important today when most lesions can be treated with low mortality. Of more importance is reoperation-free and event-free survival. Event-free survival includes not only freedom from reoperation but also survival without other major complications such as congestive heart failure, infective endocarditis, serious arrhythmias, or the development of moderate or severe stenotic or regurgitant valve lesions, the assessment of