# MORTALITY AND MALDEVELOPMENT

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## Part 1
## Congenital Cardiovascular Malformations

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Springer

A C.I.P. Catalogue record for this book is available from the Library of Congress.

ISBN 978-1-4020-5917-9
ISBN 978-1-4020-5918-6 (e-book)

Published by Springer,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

*www.springer.com*

*Printed on acid-free paper*

To my Wife–

*Bella Briansky Kalter*

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CHAPTER 1

# INTRODUCTION

Despite intense study during the 20th century, at its end the causes of the great majority of congenital malformations were still unknown. Several means had been used to try to remedy this unsatisfactory situation, a major one being the epidemiological approach, that is, by analyzing patterns of occurrence and association. Epidemiology is defined as the study of "the distribution and determinants of health-related states and events in defined populations" (Last 1988); which in the context of malformations refers to examining whether and how such abnormalities, especially particular types, may be related to time, place, circumstance, and condition; for the purpose of clarifying etiology and, implicitly, preventing them. Studies of these relations have grown in number and variety, and it is an object of this writing to describe the most significant of them, and to consider efforts to achieve this end.

This is a worthy and far-seeing objective, but a purpose of the writing as well, of more immediacy, is to bring into focus the connection of death and congenital malformation, so as to acknowledge and assess the advancement time has brought in dealing with the problems of infant mortality.

CHAPTER 2

# PRENATAL AND INFANT MORTALITY

Consideration of congenital maldevelopment must begin by recognizing its close association with early death, fetal and infant. Without examining this association an etiological picture of congenital maldevelopment can scarcely be adequately depicted. And in turn, since understanding of such deaths is needed to lay the foundation for continued discussion of our subject, knowledge is required of what this mortality is and what are its dimensions, causes, and correlates.

## A FEW DEFINITIONS

Let's first consider the deaths of interest here: those that occur before birth and those in the year after birth. Those that happen before independent life is attained, at about the 20th week of pregnancy, are called abortion or spontaneous (in distinction to induced) abortion, and those that happen after the 20th week are called fetal deaths.

While abortion is important, it is fetal deaths that are primary at this stage of the discussion; and like other deaths mentioned below they are subject to a series of dichotomies. They can occur early or late, i.e. from 20 up to 28 weeks of pregnancy, or at 28 weeks or later, the latter also called stillbirth. The frequency of stillbirth is reckoned as the number per 1000 total births, i.e. stillbirth plus livebirth.

Death of liveborn children in infancy, i.e. before 1 year of age, is of especial concern here (why that is so will be dealt with later). For reasons also to be gone into, this too is divided, into neonatal mortality, death in the first 4 weeks after birth, and postneonatal mortality, death in the remainder of the year. And last, the rationale for which will soon be described, neonatal mortality is itself divided into early and late, i.e. during the 1st week, and in the 2nd through 4th weeks after birth. The frequency of infant death is calculated as the number per 1000 live births.

## THINGS NEEDING CLARIFICATION

Matters taken for granted today not long ago were problematic. Merely to define 'live birth,' for the purpose of establishing international and other jurisdictional uniformity of reporting of facts and figures, had to contend with national differences in history, culture, and practice. Clear definition was especially needed for

distinguishing between stillbirth–children dead at birth–and those dying in the first few minutes after birth. [The early confusion can be seen in the suggestion made by Ballantyne (1902), a pioneer in fetal pathology, that the term 'stillbirth' be restricted to the fetus born alive and dying before the establishment of pulmonary respiration, and 'dead birth' for the fetus born without life.]

As broadly defined by the 1950 assembly of the World Health Organization, live birth is the "complete expulsion or extraction from the mother of the product of conception, irrespective of the duration of pregnancy," etc. But because of different conventions these criteria were not all accepted by health authorities everywhere, and variable interpretation of what constitutes a live birth continued. For example, it was unclear whether a child that gasps once and then dies was a live birth or a stillbirth; or whether a death within the first day of life, before the legal time for birth registration in a given locality, was a live birth or a stillbirth. Depending on custom and law the answer differed. These today may sound like trivial matters, but never have efforts to relinquish authority to set national standard and practices been a slam dunk. As we see every day even in the 'one world' of modern times.

Also difficult was defining 'fetal death,' the term sometimes used for 'stillbirth,' since no qualification regarding time of occurrence had been mentioned by the World Health Organization assembly; hence the earlier practice of not differentiating fetal death from spontaneous abortion persisted, and both continued to be reported together. This changed when death before the fetal age of viability came to be called spontaneous abortion–even though there's nothing 'spontaneous' about it. Nor is 'viability' a divine given; until fairly recently it was usually held to begin at 28 weeks of pregnancy after the onset of the 1st day of the last menstrual period (given the acronym LMP by obstetricians). But as advancement in medical technology succeeded in keeping many younger fetuses alive the age of viability was adjusted; until at present it is widely accepted that spontaneous abortion is death before 20–22 weeks of pregnancy; and stillbirth or fetal death is death in utero after this time.

## PERINATAL MORTALITY

Establishing these limits had an unforeseen benefit. Dividing fetal and neonatal death each into early and late encouraged the causes of death during these intervals to be examined separately; which led to the revelation that the causes of late fetal death and early neonatal death were greatly similar. From this perspective these deaths were thus seen to form a unit, and in recognition of this fact it was given its own name: perinatal mortality. Recognition of this similarity led to the further discovery, already implicit, that the causes of perinatal mortality were largely different from those of late neonatal and postneonatal death.

## FREQUENCY OF INFANT MORTALITY

How often infants die is a complex area of study, and knowledge of its changes and variations in time and place is integral to exploration of its causes. It is almost intuitive that the well-being of a society is indicated by the health of its children.

Years ago it was declared that "infant mortality is the most sensitive index we possess of social welfare . . ." (Newsholme 1910), and more explicitly, that "infant mortality is so much influenced by social conditions it has come to be regarded as a reliable index of standard of living" (Baird 1947).

By this standard the 20th century gave stunning testimony of vastly improved living conditions, with remarkable increases in the rate of infant survival in many countries and parts of the world during that period. Marvelous also was the rapidity of this achievement, especially as compared with the virtual stagnation during preceding times.

## A BRIEF HISTORICAL SUMMARY

Two or three hundred years ago, as judged by the handful of existing European records, the toll of childhood death on that continent was unbelievably high (one can only imagine what it might have been elsewhere). These sources–from Vienna, London, Sweden, France–disclose that in the mid-18th century about one third to one half of all liveborn children died in the first year or two of life.

The general record of still earlier times is less dependable, but relatively reliable information may be provided by European ruling families. Genealogical records of this privileged group not unexpectedly show superior infant mortality rates, in the 16th century about 20–25%, deteriorating a bit in the early 17th, the time of the Thirty Years War, but recovering in the next century to about 15%.

Leaping ahead to premodern times, throughout the 19th century progress was slow and irregular. In London e.g. the infant mortality record was no better in midcentury than at its beginning. And with some few exceptions, even in the last several decades and into the first years of the 20th century, it decreased little or not at all, being about 10–20% in parts of Europe.

The US got off to a slow start, with an infant mortality rate of about 25% near the end of the 19th century, but making some progress it reached 16% at its end. In some cities it fell from 30% to about 20% in the same few years; in New York City e.g. it was about 30% in 1880 and fell to 10% in 1913.

## THE FREQUENCY OF NEONATAL MORTALITY

Even sparser than early information of infant mortality as a whole is that regarding neonatal mortality, i.e. death in the 1st month. But strangely and in seeming inconsistency with the high infant mortality rate, it appears to indicate that neonatal mortality was relatively infrequent.

Thus in mid-18th century Vienna and London the neonatal mortality rate was 65–75 per 1000 live births, about as it was in ruling families a century earlier. And decades later, in late 19th century Boston and New York City, it was no better, at 80–100 per 1000. Which was also true in the large cities of Europe in that later period, 10% dying neonatally (significantly, most of these on the 1st day of life).

From this record it becomes obvious that in these early times most infant deaths occurred postneonatally, in the 2nd through 12th months of age. As can be deduced

from numbers cited from that time, about 80% occurred in the latter period, for a neonatal-postneonatal ratio of about 1:4. [The figures given above were largely derived from the unsurpassable early classics in neonatology of Graham (1908) and Holt (1913), and Brownlee's (1925), Clifford's (1936), and Peller's (1948) informative articles, McKeown's (1976) invaluable book, and several internet web sites.]

## THE 20TH CENTURY

The generally stagnant infant mortality picture of the later decades of the 19th century gives few signs of the impending quickening. Nor do European and US figures even at the start of the new century give any hint of the great change in the offing. The infant mortality rate in England in 1901, 151 per 1000 live births, was virtually identical with that of 1861. The record for US areas providing information in 1900 was no better, although greatly varying, from 121 in Michigan to 198 in Rhode Island. But in the next 10 years or so the rate fell dramatically–in England and Wales from 154 to 105, in New York City from 162 to 109, etc., etc.–foretelling the fairly steady decrease experienced in many countries of the world throughout the century.

A few examples contrasting the early and last years of the period demonstrate the dimensions of this extraordinary happening. The infant mortality rate per 1000 live births in Sweden in 1900 was 99, in 2000 it was 3.5; in France in 1900 it was 161, in 2001 4.5; in the US in 1900 it was 133, in 2000 6.8. This radical shift was true to one degree or another in almost every European country and in many other parts of the world as well, many achieving asymptotic eradication of infant mortality, others with much left to accomplish. So low in fact was the rate in some countries at the end of the century–in Sweden, as noted, 3.5, in Japan 3.9, in Finland 3.8–it seemed virtually further irreducible.

The immediate reasons for the decreases (the declines for the US are found in Table 1) are of course the early great improvements in living conditions–social, physical, medical–occurring first in advanced countries. But beyond these obvious, and it may be partial, explanations others must be considered. Some fraction, relatively small perhaps, may be connected with temporal shifts in distribution of several attributes associated with mortality, namely, birth rate, birthweight, maternal age and parity, congenital malformation. These matters will be discussed below.

Table 1 depicts the steep fall in the frequency of infant mortality and its components in the US over the course of the 20th century, from 1st-day to postneonatal deaths. But the pace of these decreases was not equal, disparities that at first were continuations of historical trends, with the greatest proportion of infant deaths occurring in the postneonatal period.

The latter proportion shifted markedly as the decrease in the rate of postneonatal deaths outpaced that of neonatal ones, at least for a time. In the US e.g., in 1915, the first year such information was registered, postneonatal mortality comprised 56% of total infant mortality, and decreased continually, till in 2000 it was 33%. Thus by

*Table 1.* US infant mortality rate per 1000 live births

| | IM | NN | PNN | ENN | LNN | D1 |
|---|---|---|---|---|---|---|
| 1915 | 99.9 | 44.4 | 55.6 | 30.1 | 14.2 | 15.0 |
| 1920 | 85.8 | 41.5 | 44.3 | 29.3 | 12.3 | 14.8 |
| 1930 | 64.6 | 35.7 | 28.9 | 27.2 | 8.5 | 15.0 |
| 1940 | 47.0 | 28.8 | 18.3 | 23.3 | 5.5 | 13.9 |
| 1950 | 29.2 | 20.5 | 8.7 | 17.8 | 2.7 | 10.2 |
| 1960 | 26.0 | 18.7 | 7.3 | 16.7 | 2.0 | 10.3 |
| 1970 | 20.0 | 15.1 | 4.9 | 13.6 | 1.5 | 9.0 |
| 1980 | 12.6 | 8.5 | 4.1 | 7.1 | 1.4 | 4.6 |
| 1990 | 9.2 | 5.8 | 3.4 | 4.8 | 1.0 | 3.5 |
| 2000 | 6.9 | 4.6 | 2.3 | 3.7 | 0.9 | 2.9[1] |

[1] 1998; IM, infant mortality, deaths in 1st year; NN, neonatal, deaths in 1st 4 weeks; PNN, postneonatal, deaths from 5th through 52nd weeks; LNN, late neonatal, deaths from 1st through 4th weeks; ENN, early neonatal, deaths in the 1st week; D1, 1st-day deaths

*Table 2.* Temporal change in percent of infant mortality intervals in US. See Table 1 legends

| | 1920 | 1930 | 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 |
|---|---|---|---|---|---|---|---|---|---|
| PNN | 51.6 | 44.7 | 38.9 | 29.8 | 28.1 | 24.5 | 32.5 | 37.0 | 33.8 |
| ENN | 34.1 | 42.1 | 49.6 | 61.0 | 64.2 | 68.0 | 56.3 | 52.2 | 53.6 |
| LNN | 14.3 | 13.2 | 11.7 | 9.2 | 7.7 | 7.5 | 11.1 | 10.9 | 11.6 |
| NN | 48.4 | 55.3 | 61.3 | 70.2 | 71.9 | 75.5 | 67.5 | 63.0 | 66.7 |
| D1 | 17.2 | 23.2 | 29.6 | 34.9 | 39.6 | 45.0 | 36.5 | 38.0 | 42.0 |

the end of the century the ratio had switched from about 2:3 to about 2:1, i.e. about two-thirds of all infant deaths then happened in the 1st month after birth (Table 2). The table also shows that within the neonatal period an increasing fraction occurred in the 1st week, and more and more of these in the 1st day; till by the year 2000 42% of all infant deaths and over 76% of early neonatal deaths occurred in the 1st day of life.

Obviously, what accounts for these shifts is the differential success in dealing with their individual causes. These age-specific mortality causes and their changes with time are discussed below. One may interject regarding the incredible increase in the proportion of natal day death over the course of the century by citing data from various times. A note early in that period reported that in New York City 13% of infant deaths occurred on the 1st day (Holt and Babbitt 1915), 37 years later in Chicago 36% died on the 1st day (Bundesen 1953), and in 1987, 57% on that day (Hansen and Kiely 1992); with a consequent shift from postnatal to prenatal factors as their basis.

CHAPTER 3

# INFANT MORTALITY

## WHAT BROUGHT ABOUT THE INFANT MORTALITY CHANGES?

With these facts as background the question turns to the basis and sources of the changes over time, first with respect to the overall frequency of infant mortality. The story begins of necessity in the mid-18th century, since that is when systematic wider recording of mortality first began and clear indications of the onset of a decline in infant mortality could be seen.

Its beginnings are associated with what the social historians call the 'agricultural revolution,' i.e. changes in farming techniques that became common in the mid-1700s. Taking England as the paradigm, since that is where the revolution had its first stirrings and where its economic and social ramifications are especially well documented, these changes consisted of technological innovations in farm machinery and methods, which gave rise to a cascade of momentous consequences–hardly foreseen, hardly imagined. Food supplies soon increased, prices fell, living conditions improved, malnutrition diminished, population grew, and infant mortality declined. It should be noted that the last started even before the advent of vaccination in the 1790s, the great direct health achievement of the 18th century.

But at the same time countervailing forces, of even greater significance for the future, were acting to suspend–for a considerable time–the last step in this series of consequences, the decline in infant mortality. These forces however consisted not, as Malthus' pessimistic prediction had it, of population growth outstripping food production: as he phrased it in his 1798 Essay on the Principle of Population, "the power of population is indefinitely greater than the power in the earth to produce subsistence for man [and] when unchecked, increases in a geometrical ratio [while] subsistence increases only in an arithmetical ratio."

No, what in fact this countervailing force consisted of was an even more crucial chain of events, another–actually a coexisting–'revolution,' the industrial revolution, the application of power-driven machinery to manufacturing. Beginning, again first and especially in England, in mid-18th century, with the invention of the steam engine and of machines for spinning and weaving cotton, it accelerated in the 19th century.

The new machinery and techniques had adverse social consequences of historic proportions, changing "the entire structure of . . . society" (Engels 1844). These

created demand for raw materials for the growing textile industry, induced farm owners to turn from raising crops to raising sheep (this too was not a novelty–is there ever anything new under the sun!–since even in Sir Thomas More's time, 200 years before, the great martyr had noted in his 'Utopia' that estates were being broken up and the sheep were eating the people), farm workers, made redundant, migrated to the cities to fill the need for factory laborers, making for urban crowding, dreadful living and hygienic conditions, and resurged infant mortality–graphically described by English urban novelists of the time, Dickens, Disraeli, Gaskell, and most shockingly by the percipient and cynical observer Engels–producing the stagnation in the record of infant survival experienced in much of the 19th century.

"Look round upon the world of odious sights–millions of immortal creatures have no other world on earth–at the lightest mention of which humanity revolts, and dainty delicacy living in the next street, stops her ears, and lisps 'I don't believe it!' Breathe the polluted air, foul with every impurity that is poisonous to health and life; and have every sense, conferred upon our race for its delight and happiness, offended, sickened and disgusted, and made a channel by which misery and death alone can enter. Vainly attempt to think of any simple plant, or flower, or wholesome weed, that, set in this fœtid bed, could have its natural growth, or put its leaves off to the sun as GOD designed it. And then, calling up some ghastly child, with stunted form and wicked face, hold forth on its unnatural sinfulness, and lament its being, so early, far away from Heaven–but think a little of its having been conceived, and born and bred, in Hell!" –Dombey and Son, Charles Dickens.

## THE MICROBASIS OF INFANT MORTALITY

Dreadful social states are but the bed in which more immediate causes of infant mortality are bred; the more proximate causes, broadly categorized, disease, environment, societal factors. As to disease, although the growing practice of vaccination in the early 19th century may have played a small part in reducing infant mortality, its effects were vastly counterbalanced by the numerous still rampant gastrointestinal and respiratory infectious diseases of childhood. Only with the profound innovations later in the century–the 'sanitary engineering revolution,' entailing what to our modern ears are mundane advancements in personal and public hygiene, water purification, improved refuse and sewage disposal, sterilization and pasteurization of milk, etc.–that death from these diseases once more began to abate; benefits it became possible to gauge when the British Registrar General and similar agencies elsewhere instituted national practices of including cause- and age-specific data in the records; thus allowing the charting of progress in preventing infant mortality and of the many and often complex elements that enter into it.

Causative agencies of the last sort, societal factors, had never been absent, as hinted at by the advantages of the ruling families noted above. But it was the intensification of them, at the dawn of the pre-modern era, that widened the gulf between segments of the population and between urban and rural areas in food resources,

housing, medical access, etc., all seriously affecting infant mortality. It is obvious and hardly needs iterating that such societal factors are numerous and complex.

## SOCIAL DISTINCTION AND INFANT MORTALITY

The individuals comprising a society, i.e. "a structured community of people bound together by similar traditions, institutions, or nationality," despite this idyllic characterization, invariably differ from one another in innumerable ways, many of which affect infant survival and other aspects of health. There are at least a half a dozen ways of classifying a populace according to these differences, most of which are highly correlated. Probably the best known is the socioeconomic grouping system, codified and given semioffical standing in Great Britain, by which populations are arranged by the profession or occupation of the head of the household (once upon a time almost always the father) into a number of serial categories. This general scheme and comparable ones, e.g. paternal income and census tract statistics, have been and continue here and there to be used to describe hierarchical patterns of infant mortality among social classes.

What are perhaps the earliest such correlative studies, using data from selected US cities for 1911–16 and from Stockholm for 1918–22, foretelling later revelations, found that paternal income as well as various social factors were related to infant mortality (Woodbury 1925, Rietz 1930; the former called "a classic study" by Yankauer 1994). A broader approach was the one mentioned above, formulated by the British Registrar-General in the years before the First World War. This divided populations into five arbitrary occupational classes, I professional, II managerial, III skilled, IV partially skilled, and V unskilled. Each class represented a related social mixture, with the whole more or less satisfactorily depicting the occupational spectrum of the population for a given period; till in time some manner of revision became necessary, as when e.g. Tanner (1978, p. 146) called it "increasingly irrelevant as an indication of the standard of living . . ."

The early studies provided a rational basis for the usually intuitively apprehended association of social level and infant well being. But they merely described a one-dimensional relation; more informative for the questions to be examined here are class comparisons over time, since they allow the identification of factors, or rather narrow the search for factors, associated with mortality. For example, while it is startling that data from England and Wales from 1939 showed that the infant mortality rate was 2.2 times greater in class V than in class I (Baird 1947), of far greater analytical and etiological meaning were historical studies that considered changes over time.

One such investigation noted that while between 1911 (pre-World War 1) and 1949–50 (post-World War 2) the overall neonatal mortality rate in England and Wales had declined over twofold, from 39.1/1000 live births to 18.2/1000, which included, as the authors commented, a remarkably similar decline among the various social groups, nevertheless the social gap had not narrowed (Morriss and Heady 1955). With respect to postneonatal mortality, although the decline in these 40 years

was over three times greater than for neonatal mortality, from 85.8/1000 live births to 11.1/1000, the gap had become even wider. For stillbirths, as for neonatal deaths, forming as they do a unit, the class differential was far smaller than for postneonatal deaths (Baird 1947). Twenty-five years later, in 1975–77, essentially nothing had changed; the class differential for perinatal mortality was 1.9, for neonatal mortality 1.9, and for postneonatal mortality 3.0 (Davies 1980).

These findings are interpreted to mean that environment, for that is what social factors essentially stand for, by 1950 or thereabouts appears to count for little or nothing in the causation of neonatal deaths, leaving the field to nonenvironmental or endogenous factors, called medical factors by some; whereas for postneonatal deaths on the contrary the environment still had some though perhaps a diminishing etiological role.

And it continued to be of importance, since a significant postneonatal differential persisted into the 1970s (Pharoah and Morris 1979), and even the mid-1990s, when the postneonatal mortality rate in Britain was about 10% greater in class IV/V than in I/II (Whitehead and Drever 1999); a persistence also seen elsewhere, e.g. in the San Joaquin Valley in California the gradient by paternal occupation extended from 3.3/1000 live births for professional and related areas to 9.0 for farm laborers and the like (Bendor et al. 1971), and the black-white ratio was about 2.3 in 2001, actually even increasing a bit from 1982-8 (Scott et al. 1998, Mathews et al. 2003).

The same facts were noted at many times in earlier years of the century in many diverse localities, first that postneonatal death yielded far more readily than neonatal death; and second that class distinction, though reduced, persisted especially for postneonatal mortality (Antonovsky and Bernstein 1977). It must be recognized at the same time that the distinction was not true everywhere; in Sweden e.g. in 1985–6 socioeconomic status and maternal education were not significantly related to infant mortality, no doubt because of the special characteristics of that nation (Haglund et al. 1993).

## THE MEANING OF THE SOCIAL GAP AND ITS NARROWING

What, then, are the attributes that perhaps explain the relation of social class and infant death, and the differences in these as they relate to neonatal versus postneonatal mortality? This is a major area of consideration, one that has exercised scholarly efforts for decades. One set of indicators, labeled “indices of social condition” includes family size, number of women manually employed, degree of poverty, and so on, but especially maternal nutrition (Woolf 1947). Also pointed to are various broad features: maternal health, physique, height, education, age at marriage, diet, family circumstances and problems, prenatal care opportunities, standard of medical and nursing care–for most of which, it hardly need be said, higher income groups are advantaged. Nor need one be reminded, such features are closely interrelated and that the better the social and economic circumstances the better the diet, health, medical care, housing, etc. But their immediate role in the death of children is murky. One explanation invokes maternal factors as promoting

successful pregnancy, birth, and survivable babies. But these in themselves are hardly adequate explanations, not affording approach to the still more proximate causal elements that one feels must exist. [Incidentally, one must remember that as these factors have mitigated in the economically advanced nations they remain as pervasive and omnipresent as ever in other parts of the world.].

## MATERNAL AGE AND BIRTH ORDER

A chain of interrelations leads to birthweight as a major factor, if not the major one, affecting infant mortality. First come maternal characteristics associated with infant mortality, prominent among them age and birth order or parity. It is long and well established that births to younger and older mothers are associated with higher than average infant mortality rates–stillbirth and neonatal mortality–as are earlier and later birth, even after adjusting for various coupled features (Friede et al. 1987, 1988). In an early example maternal age of less than 20 years was associated with an almost 7% disadvantage vis-à-vis the average, first births similarly about 6% (Yerushalmy 1938). It is not surprising that the correlates of these maternal features, through whose agency the effect on infant mortality is exerted, are many and complex. Obvious ones are socioeconomic factors that promote or delay early marriage, as was indicated by a multivariate analysis of various maternal factors showing that only social class gradient was correlated with mortality (Feldstein and Butler 1956).

Through what pathway social forces acted was unclear, but one emerged as important. Various analyses found that maternal factors such as age, parity, race, and socioeconomic status were all associated with infant mortality through their relation to infant birthweight. This thus appeared crucial for mortality, but again exactly how so was not clear (Shah and Abbey 1971, Elwood et al. 1974). [Incidentally, it is interesting that so mundane a matter as birthweight (isn't it so that almost the first thing asked of a new mother is, what did he weigh?), of such profound implications, should have had no great appreciation until relatively late in medical history. Tanner (1981, p. 254 et seq.) gave a detailed account of the beginnings and development of the practice of weighing newborns in the mid-18th century, and Cone (1961) a summary of the story.]

CHAPTER 4

# BIRTHWEIGHT AND IMPAIRMENTS

## INTRODUCTION

Until something better comes along, birthweight seems to be the best measure of fetal maturity. Or to put it more elegantly, while the outcome of statistical evaluations may be suspect, until gestation estimation is better refined there seems, even at the onset of the 21st century, to be no problem-free and conveniently applied alternative to birthweight as a measure of fetal maturity; and no better stick to use in relating states of maturity to mortality. The association of birthweight and infant mortality, especially perinatal and neonatal mortality, is the subject of innumerable studies and musings; it is the ramifications and implications of this association that are of greatest relevance and interest here. Which raises the topic of the classification of disturbances of fetal growth.

From early in the 20th century infants were regarded as immature if they weighed less than a certain amount at birth. This amount was considered to be 2275 g (5 lb) by Holt and Babbitt (1915) and 2500 g by Williams (1915), but it is obvious that such delimitations must already have been in existence for some time, since even in mid-19th century infants weighing less than 2.5 kg were regarded as immature or pathological (Tanner 1981, p 259). Ylppö (1920), who is often cited as originating this concept, was clearly a latecomer to it.

The borderline of ponderal normality is now widely held to be 2.5 kg at birth, and offspring of less than this amount labeled as being of low birthweight (LBW); the rationale for this, although debated, being that it is at approximately this point on the Gaussian distribution of birthweight that elongation to the left begins and that birthweight-specific infant mortality begins to increase. [For various reasons the latest view defines LBW as below the 10th percentile of birthweight for gestational age.] Soon afterward (i.e. 30 years or so later–reason, as the saying goes, is a creeper) the realization began to dawn that underweight at birth may not be due solely to retarded prenatal growth, i.e. 'immaturity,' but also to being born early, i.e. 'prematurity.' These terms will be used below in these senses (though at present the favored ones are intrauterine growth retardation or IUGR and preterm birth, respectively).

The complication now enters the picture, that these forms of smallness are not mutually exclusive, since not all small babies are born early and not all babies

born early are small. An early realization of this fact noted that "7.4 per cent of white babies are mature in respect of birthweight but are below 38 weeks' gestation and, conversely, 3.3 per cent of live born babies may be mature in duration of gestation and, nevertheless, below the established birthweight level for maturity" (Taback 1951). The same overlapping was seen in a large number of births in 1957–9 in New York City, where "over 60% of all live births of less than 37 weeks gestation weighed more than 2,500 gm (5 lb 8 oz) at birth, and 45% of infants weighing 2,500 gm (5 lb 8 oz) or less at birth were 37 weeks or more gestation" (Yerushalmy et al. 1965). The importance of this recognition, that there are varieties of weight insufficiency and, then, of attempting to distinguish between them, lies in the fact that their causes and consequences for mortality and morbidity differ (Kramer 1987). The consequence of concern here is mortality.

If, as it is universally accepted, LBW and neonatal mortality are closely associated, if not causally related, there is a class of conundrum (discussion of which may perhaps be an aside, but will nevertheless be indulged in) that may aid in understanding etiological matters pertaining to this causal network. Several entirely disparate situations, such as maternal smoking, elevated altitude, twinning, black birth, etc., have in common the inconsistent and puzzling fact that they are associated with LBW but not with increased neonatal mortality. The paradox, which some have explained as an artifact resulting from the use of inappropriate statistical analysis or incorrect denominators (Wilcox 1993, Joseph et al. 2004), is to be understood by considering that LBW can be due not only to intrinsic but also to adventitious factors, and that weight decrement due to the latter does not entail increased mortality risk.

Another way of saying this, it seems to me, is the explanation offered by MacMahon et al. (1965), with regard to maternal smoking, namely that smoking (the adventitious factor they considered) shifts the birthweight distribution to the left, hence the mortality of underweight children of smoking women is not increased because the weight-impairing circumstance does not affect degree of maturity; an explanation supported by the fact that underweight neonates of smoking mothers caught up in weight by age 10 months or so (MacMahon et al. 1965), and which may also serve to clarify some of the other puzzling examples named above. (Credit must be given where credit is due: once again a prior understanding of this phenomenon had been overlooked, when Eastman 1947, regarding twins, another 'adventitious' circumstance, commented that "such infants are almost always of greater gestational age than their individual weights would indicate and hence have a better chance of survival." He failed however to appreciate the fuller significance of his observation.)

Also to be gleaned from these considerations is that immaturity is a lesser mortality risk factor than prematurity, a matter to be discussed further below, along with other thoughts about the 'conundrum.'

A secondary matter concerns the definition of subnormal weight. Peckham (1938) believed that a single standard in this regard was precluded by weight differences associated with race, age, parity, and sex, and therefore regarded separate criteria as

necessary. Eastman (1947) recognized that an iron-clad definition was unrealistic; and on the basis of certain developmental criteria asserted that "the figure for negro infants should be nearer 2350 g." Anderson et al. (1943) on the basis of other considerations agreed, and suggested that separate weight standards be established for whites and blacks, with 2300 g considered as the lower limit of normal for blacks. This matter raises a number of questions, especially regarding gestation length and its relation to race and ethnicity, which will be explored below.

From the argument above interesting questions can be asked; e.g. can one infer that male newborns, which weigh more but have a higher infant mortality rate than females, are constitutionally handicapped? (It is remarkable to read that 150 years ago it was known that even at the same birthweight more boys died than girls [Tanner 1981, p 258].) Or that persistent black-white LBW and neonatal mortality differentials in the face of temporal improvement in several risk factors–nutrition, medical care availability, etc.–hint at the existence of intrinsic or physiological bases of lowered birthweight, possibly including tendency to preterm birth? Such questions are important for inquiry into the interrelated causation of LBW and mortality.

## THE FREQUENCY OF LOW BIRTHWEIGHT

Accepting the usual blanket criterion of low birthweight as weight at birth of less than 2500 g, we ask how often underweight babies are born? Looking at the matter overall, since the time of its apparent first recording in the US in mid-20th century, aside from insignificant shifts its frequency has hardly budged, varying from 7.5% earlier to 7.8% at its end; with even the slight increase perhaps an artifact due mostly to the increase in reproductive technology-caused multiple births and births to older women, with their greater LBW risk. The races were different in this respect, with unsystematic fluctuations from 6.8 to 7.1% in whites; while in blacks on the contrary the rate rose fairly steadily from 10.2 to 13.3% at its close.

The frequency of a further category, very low birthweight (VLBW, $<$1500 g, $\sim$3.3 lb), with drastic consequences for mortality and morbidity, grew in both groups, but minimally for whites, ranging from 1.0 to 1.2%, with the increase confined entirely to the last decade of the century, while for blacks it increased steadily over the period, from 1.5 to 3.1%. VLBW is a special problem because it is predominantly the product of preterm birth (see below), and is and probably for a long time will continue to be largely intractable.

## THE CAUSES OF LOW BIRTHWEIGHT

The study of birthweight properly begins with a description of the growth of embryos and fetuses in relation to chronological age, a focus of human embryology; a term now thought passé, and superseded, but without true gain, by 'developmental biology.' Such study has shown that during midfetal life growth takes a straight line, negative departure from which early in the 3rd trimester leads to growth

retardation, whose degree as seen at term depends on when the departure from normal occurs (Gruenwald 1969).

This impairment of fetal growth can ensue from many things, intrinsic and extrinsic, which have been examined and written about ad infinitum. Reduced birthweight, as learned above, is due to reduced intrauterine growth or to too early birth, immaturity or prematurity, respectively. The possible causes of these forms of birthweight insufficiency are legion. An exhaustive enumeration of the potential factors, said to be "almost limitless," included: genetic and constitutional factors, demographic and psychosocial factors, obstetric factors, nutritional factors, maternal morbidity during pregnancy, toxic exposures, and poor antenatal care. Kramer (1987) listed forty-three different factors as associated with immaturity and the same number with prematurity, with much overlap between them, many nonspecific and indirect. But while sharing many social, economic, demographic, and other risk factors they are considered to differ in etiology and proximate determinants, though few studies have attempted to establish the distinction.

Of this host meta-analysis found that three maternal factors stood out, cigarette smoking, poor gestational nutrition, and low prepregnancy weight (but not height), which alone accounted for about two-thirds of the known causes (Kramer 1987). Of them only smoking is specific and concrete enough to have had its effects on gestation well evaluated. Maternal cigarette smoking especially during about the 3rd trimester of pregnancy decreases mean birthweight and increases the frequency of LBW, in a nonlinear manner, even when associated risk factors are discounted; with the effects about doubled in blacks compared with whites, corroborating early findings (Yerushalmy 1964), mostly due to retarded fetal growth and less to early delivery.

While there is little doubt of these consequences, more recent data substantially modified the perspective. A past estimate put the fraction of LBW due to smoking at 36% (Kramer 1987), but a recent evaluation (Magee et al. 2004) found a far lower etiological fraction, 11%, in nearly 80,000 women of whom about 12% were smokers. Also smoking accounted for a mere 1.7% of VLBW infants, indicating the major effect to be on immaturity. The smaller figure is probably due to different habit or different population, but in any case is a sign of social consciousness of the problem. Further hint of change came from a nationwide survey finding a significant decrease in smoking prevalence (Ventura et al. 2003) and from a New York Times item of 5/12/04 reporting an 11% decline in cigarette smoking in New York City from 2002 to 2003, occurring in all ages and ethnic groups.

## LOW BIRTHWEIGHT AND INFANT MORTALITY

The factors associated with LBW are largely similar to those associated with infant mortality, and the task has been to tease apart these many determinants in the search for their primary components. But it is to LBW per se that at present far the greatest responsibility for infant mortality is assigned. Even earlier it was common

knowledge that 'immaturity' is the principal cause of death in the neonatal period. As Baird (1964) wrote, "Although fewer than 10 percent of babies weigh less than 2,500 grams . . . at birth, they provide more than 50 per cent of all deaths during the first week of life . . ." In recent years these proportions have risen and lately in the US nearly two-thirds of all neonatal deaths were associated with LBW; and VLBW, at 1.4% of live births, for 19% of all LBW, itself for about half of neonatal and one-quarter of infant mortality. Two-thirds of LBW and about 12% of births were preterm (a subject to be discussed further below), the latter responsible for 70% of US perinatal mortality.

Both immaturity and prematurity (as gauged by birthweight and gestational age, respectively) are related to neonatal mortality, but which has the greater role is difficult to gauge since they are closely almost inextricably linked (difficult especially because in most reports LBW of both origins were reported together). In fact there once seemed little reason to attempt individual assessment, since ". . . there is little to choose between them as indices of the probability of survival . . ." (McKeown and Gibson 1951). Their joint action was of interest however, and calculations were made of it, described by formulas and diagrams, which though intended for practical purposes, require sophisticated judgment to interpret and apply (Karn and Penrose 1952).

Nonetheless, although birthweight and gestational age may be correlated, the question remains which of them contributes more significantly to mortality. An early analysis of livebirths in New York City in 1957–9 sorted this problem out by comparing neonatal deaths in those of 2500 g or more birthweight who were either less than 37 weeks or 37 weeks or more of gestational age, finding overall almost three times the mortality rate in the former than the latter, i.e. prematurity the more lethal factor than immaturity (Yerushalmy et al. 1965). When the same analysis was applied to congenital malformations it was seen that both of these groups had approximately the same frequency of severe malformations. These assessments to my knowledge have not to the present been rigorously verified.

In fact different answers were later supplied. One study showed that birthweight was responsible for a vastly preponderant 90% of the variance in perinatal mortality, while the share of fetal age was a mere 5% and the interaction of both 2–3% (Susser et al. 1972). The question rested at these points for some years; when an analysis based on weight distribution within gestation age brackets, while confirming the strong link between birthweight and perinatal mortality, asserted that age is a "powerful predictor of . . . perinatal survival . . ." (Wilcox and Skjœrven 1992), but provided no specifics. This conclusion seems to be supported by the fact that preterm births are at increased mortality risk; but whether so because of inadequate weight or of elements of immaturity is still not satisfactorily settled leaves the puzzling question no further advanced.

Another puzzle, underlying all others, is the apparent inconsistency that despite the close relation of LBW and infant mortality, while over the years relatively the former has only slightly changed, the latter has plummeted.

## SMOKING AND INFANT MORTALITY

Maternal cigarette smoking has been associated with increased infant mortality for many years (Meyer 1977, Joseph et al. 2004). The numbers are startling and appalling. Recently infant deaths were found it to be 40% higher in offspring of smokers than of nonsmokers, and smoking accounted for 5% of all infant deaths in the US (Salihu et al. 2003). As seen above, smoking also causes an increased rate of LBW, long ago found to be about twice as great in black smokers as in white (Yerushalmy 1964), which is probably among the main reasons for the excess of infant deaths in blacks. The contradiction, also noted above, that mortality rates are lower for the LBW babies of smokers than of nonsmokers, has been resolved to the satisfaction of some by various statistical approaches, with the upshot that at present it is believed that infants of smokers have a higher mortality rate than of nonsmokers at all birthweights and gestational ages (e.g., Wilcox 1993, Joseph et al. 2004).

The current difference of opinion centers on the question whether LBW is on the causal track of increased infant mortality. See Wilcox (2001) for an exposition of the argument.

## LOW BIRTHWEIGHT, MORTALITY, AND RACE

From the time LBW was first subject to epidemiological analysis its frequency has continued to be roughly twice as great in blacks as in whites, the same approximate disparity as for infant mortality rate. But while infant mortality greatly declined in the last half of the 20th century LBW changed little or not at all–in defiance of the inverse relation between weight and mortality; a seeming anomaly some attribute in part to improved medical care (Lee et al. 1980a), but not likely to account for any but a small fraction of it. Surprisingly, however, while the B-W infant mortality and LBW ratios have wavered but little, the infant mortality-LBW ratio has greatly decreased, although maintaining a remarkably close similarity in blacks and whites.

The relative stability of the LBW frequency during this period contrasts with the great increase in the frequency of VLBW, but with a much greater increase in blacks than whites, 20 and 11% respectively (also see Alexander and Slay 2002). This has caused a shift in the basis of the mortality rate from LBW to VLBW, i.e. the former has been outdistanced by the latter as a cause of infant mortality (e.g. see Lee et al. 1980).

Because undersize at birth and its associated increased infant mortality are conspicuously associated with race and ethnicity, it is appropriate to discuss the role of LBW in the mortality disparity between racial groups, especially but not only between blacks and whites in the US. Blacks and whites differ in several reproductive parameters: mean birthweight, frequency of LBW, mean duration of pregnancy, and frequency of preterm birth. It was repeatedly noted throughout the 20th century that black babies at birth weigh less on average than white babies

(Riggs 1904, Anderson et al. 1943, Kramer 1987, David and Collins 1997). It was also recognized early that LBW, using birthweight of less than 2500 g as its measure, is about twice as prevalent in black births as in whites, a disparity that continues to the present day (Kleinman and Kessel 1987, Miller and Jekel 1987, Alexander et al. 1999, Pallotto et al. 2000, Arias et al. 2003).

The basic fact, to state it again, that while both black and white infant mortality rates continually declined throughout 20th century, the proportional discrepancy between them remained and is still largely unchanged, the black-white ratio in 2002 being at a near historical high of 2.6; and to some large measure this sad state can be traced to the fact that LBW and especially VLBW rates in blacks continue to exceed those in whites.

However, two linked factors complicate the meaning of these racial differences and of the relation of birthweight to perinatal mortality, namely that the mean duration of pregnancy (measured by LMP), as discovered years ago, is about 1 week less in blacks than whites (Anderson et al. 1943, Erhardt et al. 1964), and that the rate of preterm birth ($\leq$37 w), despite the recent narrowing of the gap, is twice as high in blacks as in whites (Taylor 2000, Demissie et al. 2001).

It was once thought that birthweight in blacks and whites could only be compared if the standard of comparison were adjusted to recognize an apparently innate racial difference, namely that black LBW infants have a lower mortality rate than white LBW infants, whereas in those of normal weight the reverse is true; a difference attributed to black babies being more mature than whites, on the basis of developmental and other considerations.

But the question, upon being reexamined in the light of new interpretations, was found to be misleading. When instead of an absolute standard of smallness a population-specific standard or fetuses-at-risk of death at each gestational age was used as the denominator this difference disappeared, and at all weights blacks had a worse mortality record than whites (Wilcox and Russell 1990, Joseph et al. 2004). This therefore eliminated the need to explain on a physiological or maturity basis the supposed superiority of small black babies. [The same resolution of the question however may not be applicable to some other weight conundrums mentioned earlier (see p. 16)]

## THE SMALLNESS OF BLACK BABIES

The major, perhaps the only, reason for the racial difference in mortality risk, it has been conjectured, is the difference in birthweight: the "entire excess of perinatal death rate of nonwhites over that of whites could be accounted for by the difference in birthweight between the two groups" (Susser et al. 1972). The question therefore boils down to the question of why the difference?

It is easy to see why, in seeking reasons for population differences in birthweight, maternal health-related behavior and socioeconomic conditions should be considered first. An early such explanation focused on the fourfold greater frequency of syphilis in black women than whites and, significant for later thought, the

many generations of inner city existence of black women as evidence "generally of physical degeneration" (Peckham 1938). Eastman (1947), perhaps feeling the need to be discreet, stated that "it is important to make plain . . . that we [*sic*] do not regard the difference . . . so much racial as economic." Baird (1964), with a broader perspective, posited what was later called intergenerational influence–the transfered effect of short maternal stature on offspring birthweight stemming from socioeconomic derivation in childhood. A suggestion supported by the finding that maternal height was closely associated with offspring birthweight (Abernathy et al. 1966, Hardy and Mellits 1977); an association already noted generations before (Tanner 1981, p 259), and more generally found earlier to act on various birth outcomes (see references in Gruenwald 1968). More recently other evidence, such as shifts in LBW frequency associated with demographic change, and the fact that the frequency of almost all causes of infant mortality was higher in blacks than whites, also supported the environmental argument (Kleinman and Kessel 1987).

Contrary voices were also raised. A large cooperative effort concluded that "attempts to account for racial differences in terms of . . . socio-economic factors fail to remove the possibility that White babies are inherently . . . heavier than Negroes" (Naylor and Myrianthopoulos 1967). Another strand of support for a genetic basis of low birthweight was supplied by analyzing birthweight by population-specific standard, discussed above, which found that "blacks would suffer excess [neonatal] mortality even if their birthweight were identical to whites" (Wilcox and Russell 1986). This was contradicted by finding, in a selected population, that only LBW blacks, not those of normal weight, had higher mortality rates than similar whites (Schoendorf et al. 1992). Race was still a significant determinant of LBW even after a number of sociodemographic factors were controlled for (Miller and Jekel 1987, Kleinman and Kessel 1987), as was found by several other studies referred to by these authors; even while some continued to believe that "factors currently used to control for ethnic differences in birthweight are insufficient to explain the observed differences" (Shiono et al. 1986a).

Support for the inherent basis of such differences in pregnancy outcome also emerged from various comparisons of birth outcome: low risk and even what were called extremely low risk black and white women (Collins and David 1990, Alexander et al. 1999), women with "remarkably similar" reproductive and social circumstances (McGrady et al. 1992), and similar educational (Schoendorf et al. 1992), and lower-income status (Friedman et al. 1993, Goldenberg et al. 1996), in which again the incidence was greater in blacks.

These studies were interpreted as showing that the environment, i.e. extrinsic sources of variance, at least those parts of it that were put to the test, are less important in producing LBW than the other half of the usual equation, nature. This has not been willingly accepted however, and the search for responsible environmental elements has continued.

Preterm births may offer some other matters to ponder. In a New Brunswick, New Jersey hospital a significantly higher proportion of black infants were born

preterm than whites or Hispanics, and thus had significantly lower birthweight than the others; despite which infant mortality and morbidity were comparable in the racial and ethnic groups (Petrova et al. 2003). Thus reduced gestational age, and multiple pregnancy, which was also increased in blacks, was not associated with increased infant death.

CHAPTER 5

# ETHNIC AND OTHER COMPARISONS

## NATIVE-BORN VERSUS FOREIGN-BORN

One means of examining these matters has been to compare US native- and foreign-born black women, on the rationale that on average genetic differences between them are less than environmental ones. Because the birth outcomes of the foreign born have consistently been the more favorable, it was assumed that the basis of the advantage lies in life style and background, study of which may reveal its nature. In some studies hints emerged of better past health and cultural and behavioral circumstances that may have partially supplied these details (Valanis 1979, Valanis and Rush 1979, Cabral et al. 1990, Wasse et al. 1994, Pallotto et al. 2000). One attempted explanation along the same line went much further and said "it may be necessary to look at not only the current life circumstances and socially disadvantaged position of US-born Blacks vis-à-vis foreign-born Blacks, but also their unique socio-cultural and political background in terms of historical perspective. . . . Foreign-born Blacks, on the other hand, have not had similar long-term exposure to socioeconomic and structural discrimination" (Singh and Yu 1996). The support for this assertion, it was believed, consisted of the "beneficial effect of immigrant status . . . [which may] serve as proxy for a host of protective . . . factors . . ." –assertions still to be validated.

Another approach to the basis of the poorer birth outcomes of black than white women came from a novel consideration (David and Collins 1997). Challenging the "genetic concept . . . of birthweight" was the fact that despite native-born blacks having significant white admixture their babies are not of lower birthweight than foreign-born black women.

There are exceptions to the usual finding that foreign-born women have advantaged births. Native- and foreign-born non-Hispanic white women in at least two cases were little different from each other in the usual birth outcomes, and the same was true of Japanese Americans (Kleinman et al. 1991, Singh and Yu 1996, Alexander et al. 1996), even though in the case of the white women the immigrants were sometimes of a lower socioeconomic status than the native born; and in another case foreign-born Puerto Ricans were at greater risk for disadvantageous birth outcomes than mainland-born Puerto Ricans (Anon. 2003).

## LATIN STUDIES

A large and rapidly increasing segment of the US population consists of Latin Americans. And they too present some puzzles. Thus, in spite of low socioeconomic status, Mexican-Americans have LBW and infant mortality rates similar or even superior to whites (Shiono et al. 1986a, Dowling and Fisher 1988, Becerra et al. 1991, James 1993, Hessol and Fuentes-Afflick 2000, Alexander et al. 2003, Sastry and Hussey 2003, Leslie et al. 2003); suggesting protective effects of "traditional Mexican cultural orientation" or "sociocultural protection from the effects of urban poverty." This 'protection' unfortunately seems to be evanescent and is confined to the first-generation children of migrants, since in a comparison of foreign and US-born Mexicans the former had the better birth phenomena record (Ventura and Taffel 1985, Collins and Shay 1994). Thus in the process of acculturation (whatever that may consist of; de la Rosa 2002) the protective factors appear to be diminished or overridden (Scribner and Dwyer 1989, Guendelman et al. 1990, Ventura et al. 2003). Would that they could be identified and perpetuated. Last, it should be recognized that Hispanic immigrants are a diverse people, and this diversity is reflected in the different birth outcomes of those from various countries (Ventura and Taffel 1985, Singh and Yu 1996, Anon. 2003).

Further puzzling are studies comparing birth outcomes in foreign-born Mexican Americans and Asian Indians; the puzzle being that although the former had socioeconomic and other risk factors similar to those possessed by blacks, they did not have increased levels of the negative outcomes, whereas the latter, who on the contrary had a marked socioeconomic advantage, had various poor outcomes (Shiono et al. 1986a, Gould et al. 2003). It is the latter that it is especially difficult to understand.

## INTERRACIAL STUDIES

The question has also been probed by comparing interracial with single-race births, with the expectation that maternal and fetal factors affecting intrauterine growth, nongenetic and genetic respectively, could thereby be separated. Finding a gradient of detrimental birth outcomes, from most to least affected in respectively infants of black parents, black mothers and white fathers, white mothers and black fathers, and white parents, indicated that fetal growth was determined predominantly but not exclusively by nongenetic maternal factors (Migone et al. 1991, Collins and David 1993). The main findings concerned the interracial births, which though intermediate in birth outcomes resembled the maternal type. Interpreting these findings was made difficult, as usual, by the entangled complex of hereditary and environmental factors influencing birthweight, although some interpretations favored the nongenetic; culminating again in the lament that "it's time to reach beyond these [conventional] variables in order to develop a better understanding . . ."

Repeated assertions that as yet unidentified impacts on pregnancy outcome must be considered took a new turn when, once again finding that neither genetic factors

nor sociodemographic characteristics could satisfactorily explain disadvantageous black birth outcomes, suggestions were voiced that new conceptual models were needed, that chronic exposure to racism, social pressures related to maternal race, the perception of exposure to racial discrimination, and such considerations, should be looked into (James 1993, Collins and David 1993, Singh and Yu 1996, Collins et al. 2000). Rather different, however, was another conclusion, namely that "... measures of material hardship and social adversity varied greatly by ethnic group but were not associated with mean birthweight, and thus may not explain the ethnic-group differences in birthweight" (Shiono et al. 1997).

The findings of another interracial study departed somewhat from others (Hessol et al. 1998). After adjusting for what was called "aggregate information on socioeconomic status," i.e. numerous potential risk factors, individual and community–maternal, paternal, infant, educational, social, etc., etc.–the full gradient described by others was not present, but risk for moderate LBW occurred only in infants of black mothers, and interracial infants only had an elevated VLBW risk relative to white ones. Thus, an erratic picture emerged from the application of what apparently were a series of bivariate comparisons.

In a similar study, of relative risks of LBW and VLBW, the often observed gradient appeared, and adjusting for some maternal characteristics modified but did not alter the overall outcome (Parker 2000). While over time LBW risk for white interracial infants improved (rather like that also noted by Collins and David 1993), there was none for black interracial infants; but, significantly, no improvement in either for VLBW risk, perhaps indicating relative insensitivity of the latter to extrinsic influences.

The upshot of this type of study was that all more or less encountered the same dead end, and all struggled to imagine what could lead them out of the impasse.

## INTERGENERATIONAL EVIDENCE

Seeking answers to the still poorly explained racial LBW disparity led to examining the possible influence of antecedent factors. Among such remote influences on infant birthweight, it has been imagined, are inter- and perhaps even multi-generational factors, especially parental birthweight. These characteristics were partly discussed above. Baird (1964) mentioned the effect of maternal stature on offspring birthweight, and earlier it was found that birthweight is related to maternal height (McKeown and Record 1954), a conclusion supported by multivariate analysis (Abernathy et al. 1966). As Tanner (1981, p 259) related, observation of this connection, long forgotten, had been made by many bygone generations.

More recently maternal and paternal birthweight were both found to be strongly associated with infant birthweight, even after control for numerous confounding variables (Little 1987, Skjærven et al. 1997, Magnus et al. 2002). The relation appeared in different ethnic and racial groups. LBW black, Hispanic, white, and American Indian women had an increased risk of VLBW and preterm infants (Emanuel et al. 1992, 1999, Leff et al. 1992, Sanderson et al. 1995), but the status

of mother and infant were in conflict, since women who were premature had a greater risk than women who were immature and the reverse was true of infants (Leff et al. 1992).

Aside from the tacitly accepted maternal contribution, the infant status results from a combination of the maternal contribution through sociodemographic attributes (Parker and Schoendorf 2002) and paternal history (namely birthweight), acting not through the uterine environment but through the fetus itself; but by what route, if not through the fetal genotype, was not discussed (Conley and Bennett 2000).

In imagining how maternal birthweight affects infant birthweight it may be supposed that the following pathway was inferred, though the conceptual route may not have been so explicitly formulated: Since LBW is associated with perinatal mortality, perinatal mortality with maternal physique, and perhaps maternal birthweight with adult size (Joubert and Gyenis 1997), it follows that maternal birthweight relates to infant birthweight (Collins et al. 2003). As for paternal birthweight, while its basis can be imagined, it is difficult to conceive of a direct connection between it and infant birthweight. Still, a weak association is sometimes claimed (Coutinho et al. 1997) and sometimes not (Collins and David 1993). Left unaddressed is the nature of the possible paternal part in this, other than by the father's genetic contribution to the fetus, which while not necessarily discernible otherwise is expressed by the active role the fetus takes in its own growth.

## PRETERM BIRTH AND PERINATAL MORTALITY

*Mcduff was from his mother's womb/Untimely ripp'd.* Macbeth V. vii.

Preterm birth, along with congenital malformation, is at present the leading cause of perinatal mortality in the US and other countries of the world (Kramer at al. 2000). There are several types of preterm birth, but the one of interest here and the most common is defined as spontaneous birth before 37 completed weeks of gestation, i.e. after a shortened duration of gestation. Its rate, not only in multiple births, but even in singletons, has continuously risen in whites and blacks in the US since about 1950, to 10.4% by 2002, 9.1 and 16.0% in non-Hispanic whites and blacks respectively, a racial differential that has persisted over time; and a rate that has increased in some other countries as well (Berkowitz and Papiernik 1993).

Causal factors considered possibly related to preterm birth have been extensively analyzed. Years ago preterm birth was not found to be associated with maternal illness, socioeconomic deprivation, and increased number of premature children (Anderson et al. 1943, Taback 1951), and later not to certain disease entities, alcohol consumption, and cigarette smoking, and perhaps marginally to maternal age, marital status, number of previous pregnancies, and short maternal height (Kaltreider and Kohl 1980, Berkowitz 1981, Kramer and Victora 2001). As of today the basis of the great majority of premature births is still not in the least explained

(Kramer 1987, Papiernik and Alexander 1999). There is familial evidence of a hereditary connection, multifactorial, of course, and thus with environmental input as well (Wildschut et al. 1991), but that little explains its recent increased frequency or racial differences.

Why being born early is associated with increased mortality is sometimes a mystery, but may be explained generally by neonatal survival depending more on maturity than size, infants with a higher gestational age at each birthweight below 2500 g having a better survival rate than infants with a lower gestational age. Thus LBW infants of greater gestational age were associated with improved survival (Allen et al. 1993).

The mystery is especially acute with reference to US black babies, who are at increased risk of preterm birth, although usually being more mature in several respects (pulmonary function at birth, neurological maturation, etc.) than preterm white babies. That black infants have a higher rate of preterm birth and a significantly shorter duration of gestation than whites are facts known since at least before midcentury and noted a number of times since (Papiernik et al. 1990, Papiernik and Alexander 1999). Nor is it true only of US blacks, since African black women with insignificant European admixture had a shorter gestation period than French women of European ancestry, even when adjusted for socioecomomic variables (Papiernik et al. 1986).

Such facts led to the belief that these differences indicate inherent racial tendencies (Susser et al. 1971, Wildschut et al. 1991, Berkowitz and Papiernik 1993). The last authors, seemingly contradicting themselves, neverthless maintained, apparently on the basis of inconsistent findings, that the higher preterm delivery rate of blacks stems from factors not "easily controlled for in epidemiological studies . . . [such as] . . . psychological stress stemming from social deprivation." Meanwhile familial evidence of the heritability of the tendency to preterm birth and study of possible genetic factors underlying it should not be ignored (Shiono and Klebanoff 1986, Ward 2003).

CHAPTER 6

# CAUSES OF PERINATAL MORTALITY

## INTRODUCTION

Study of the causes of fetal and neonatal mortality has a long and respectable history; but a torturously slow record of accomplishment. Beginning soon after the start of the 20th century obstetricians, pediatricians, and pathologists, in their attempts to discover and understand the causes of these untimely deaths, based on clinical finding and autopsy examination identified a mixed bag of maternal and fetal factors judged relevant. Clinically and hence pragmatically oriented, as most early studies were, the factors most emphasized were those considered preventable, through the only medium available then, and for many years to come, improved maternal care. For many of the causes the task was limited by their societal basis, made especially evident by the condition often heading the list, syphilis.

What was the background against which these initial attempts to identify the more proximate causes of this mortality were made? The neonatal mortality rate had decreased greatly in the first decades of the century, in the US e.g. down 50% from 1920 to 1950. Alleviation and elimination of some of the extrinsic causes partly explain the decrease, among them control of the major commununicable diseases, especially pneumonia and influenza (Wolff 1944, Terplan 1953). But though infant mortality had been drastically reduced, "little reduction has occurred in mortality for infants under 2 weeks of age [and] further reduction will depend on a determination of the factors responsible for these deaths" (Bundesen et al. 1938); and a decade later the same lament prevailed: "... improved conditions of public health and advances in medical knowledge ... resulted in a tremendous reduction in mortality during later infancy [but] exerted a much smaller influence on mortality during earliest infancy ...." (Potter and Adair 1948). But betraying pervasive pessimism a short time later it was asserted that "the general causes of perinatal mortality are the same today as they have been through the centuries and as they are likely to be in the future, and they seem to be the world over" (Potter 1954).

The earliest studies of the causes of these deaths were clinical, and reflecting this orientation dealt with the related major problems of the period: infectious disease, difficult childbirth, toxemia, prematurity, etc., plus many others labeled 'unknown' and 'various,' the last two in fact together accounting for almost 30% of one early

compilation (Williams 1915). Toxemia and prematurity were more definite, the latter not more manageable however (recognized at that time to be due to "inability of the poorly developed child to lead an extra-uterine life," and which now as then remains an important component of perinatal mortality).

Far down on the enumeration of the causes of death in most of the earliest reports were congenital malformations, rarely named, described, or analyzed. Williams (1915) differed from most others in his era and even later in naming and specifying a small number of deaths "from congenital deformity," but realizing that such anomalies "originated during the first weeks of pregnancy" and that prenatal care could not be expected to reduce their number, gave the greatest share of attention by far to seemingly preventable causes of death, a perspective that continued for many years. The perceptiveness of the comment must be noted, since it anticipates a general precept of teratology explicitly enunciated only years later.

Another early account further illustrated the difficulties of attempting to grapple with the problem. Heading Holt and Babbitt's (1915) list were congenital weakness, related to the physical condition of the mother during pregnancy, and accidents of labor, these two alone accounting for over half of the deaths. Next came infectious diseases and an assortment of miscellanea, among them a few malformations, especially of the heart and nervous system. The article's summary however concurred with others then and for years to come in giving first place, responsible for almost half of the deaths, to prematurity, defined as births of less than 45 cm in length or 5 lb in weight.

In Chicago, during ensuing years a great reduction in neonatal mortality was achieved by the improved conditions in the delivery room, which reduced birth trauma and anoxia (Potter 1954). Remaining unsolved however were prematurity and congenital malformation which decreased absolutely while increasing relatively (Potter and Davis 1969). It was in fact the small fraction of premature offspring that continued to constitute the great majority of mortalities, in one report 61% of the 1.7% that were premature (Calkins 1950), and in another almost one-third of deaths that were associated with prematurity (Potter 1954).

Control of infectious diseases and maternal toxemia were particularly of early benefit while improved obstetric technique lowered birth trauma with its harmful consequences, fracture, intracranial hemorrhage, etc. But other large parts of the difficulty, prematurity and its concomitants, associated principally with low birthweight, had not partaken of these advances, and of course congenital malformation continued as the most fundamentally intractable of all.

By the 1950s the growing conspicuousness of malformations demanded acknowledgment. In recognition of recent discoveries-the teratogenicity of maternal rubella (Gregg 1941) and of experimentally induced dietary deficiencies (Warkany 1947)–the fact that external forces can cause congenital anomalies was growing in acceptance; whose appreciation led to statements such as "experimental embryologists . . . can explain how most anomalies develop but not why [so that] we can no longer assume a passive attitude toward congenital anomalies" (Simpson and Geppert 1951). No suggestion, of course, was made as to what 'active' attitude there should instead be.

The new perspective was gaining ground: "... considerable evidence has accumulated to show the dependence of the young embryo on external environmental factors ... (Terplan 1953); malformations "may be the result of genetic factors or of external factors ..." (Crosse and Mackintosh 1954). In evidence of this new regard, the latter authors authors listed in some detail the malformations found in perinatal deaths in Birmingham, among which brain and spinal cord defects were predominant, not unexpected for a region with a high incidence of neural defects. Despite which they could do no better than divide causes of deaths simplistically into complications of pregnancy, complications of labor, and postnatal complications.

By and large, though, the 1950s were generally a period of relative quiescence in the further understanding and control of the causes of perinatal and neonatal mortality; reflecting perhaps the slowdown in the rate of these deaths in several countries (Chase 1967). In Chicago, e.g. the slight improvement if any in the mortality rate in this period could be attributed to the significant decrease in mortality from trauma and a lesser one from prematurity, while anoxia and malformations continued unabated (Potter and Davis 1969). Anoxia was also a major cause of mortality elsewhere, e.g. in Sweden, but as ever a leader in mortality prevention, the rate in this country decreased by about 26% in this decade (Lindgren et al. 1962). Thus, by the end of the 1950s, in the US and a number of European countries, the leading immediate causes of neonatal deaths were respiratory difficulties and birth injuries, but with congenital malformation close behind (Chase 1967).

## PATHOLOGY STUDIES

I digress momentarily to introduce a strand of study of early infant death that complements the clinical one. It is useful to return to earlier periods and consider an overview of the general perinatal mortality situation and how it changed with the years, by seeing it through the eyes of pathologists. Autopsy study, as mentioned earlier, is the other track taken in the study of early infant death. Early interest came from fetal pathologists, many of whom intriguingly were women. Their major focus brought another orientation to the problem–the careful description of autopsied material and clear-cut inventory of the causes of the mortalities as seen from this viewpoint–all but devoid of analysis however. But naturally it was structural phenomena that were often given the greatest attention, and thus it is such reports that will be especially noted here.

The earliest example I have discovered is Clara Dunbar Tingle's (1926) report of material collected in 1923–5 at a Sheffield hospital for women, of "still-born viable fœtuses, or children dying within seven days of birth" (her name changed after marriage, following the custom of the day, to Clara Cross). In an introductory word she conceded the then state of ignorance, and allowed that "a sounder knowledge of fœtal pathology" would be beneficial, but, it is not to be wondered, went no further. Agreeing with the then current convention she divided causes into maternal, placental, and fetal states, but the pathologist was in evidence in giving almost exclusive attention to the last, comprising traumatism at birth, infection, and anomalies.

In 160 consecutive autopsies (stillbirths and neonatal deaths not described separately) there were only a small number of malformed specimens. This is not surprising since two-thirds of the deaths were due to traumatic occurrences at birth. Omitting those and the few instances of death attributed to fetal infection there were six instances (15%) with malformations, four with cardiovascular malformations of various sorts (two with "definite signs of Mongolism," as Down syndrome was called then–remarking incidentally that it had been Garrod (1899), the 'inventor' of inborn errors of metabolism, who pointed out the association between cardiovascular malformations and Down syndrome); in addition there was an achondroplastic dwarf (whose family was free of dwarfism) with no nonskeletal defects, and one with congenital goiter that also had a lumbosacral spina bifida and other anomalies, but none with anencephaly–this a surprise, because Sheffield had an appreciable incidence of this condition (Sunderland and Emery 1979). Her discoveries were in agreement with the prevailing findings of the day, that most perinatal deaths were due to excessive trauma during delivery.

The next significant study of the causes of perinatal death–made by another woman pathologist, Edith L. Potter–appeared some years later (Potter 1940). It examined the causes of death of 2000 stillbirths and neonatal deaths (almost half of less than 1 day and nearly three-quarters less than 2 days old) collected in 1934–40 from Chicago sources. Not too amazingly, in 44% the reason for death could not be established; and in another 34% it resulted from intracranial hemorrhage and asphyxia, no doubt due to birth trauma. The next significant cause of death was malformation, whose frequency, omitting those due to trauma, was 12% in stillbirths and 20% in neonatal deaths, 13% in premature and 34% in term ones. By far the most frequent, almost half, were those of the central nervous system (hydrocephalus and anencephalus), about one-tenth cardiac, and the remainder a miscellany of major defects, and a small number of benign or minor defects, such as clubfoot, cleft lip, polydactyly, etc. Incidental findings were that malformations occurred twice as often in whites as in blacks and were 1.5 times as common in females as in males, the latter no doubt due in part to female anencephalic predominance. A subsequent report was no more informative (Potter and Adair 1943). The predominant identified cause of death thus continued, even at this period, to be trauma at delivery.

Gruenwald (1941), as befitted an embryologically minded pathologist, in a lengthy table listed every anatomical defect–malformation and deviation, single and combined–in autopsies of a wide range of ages, even beyond infancy however, which greatly diminished the usefulness here of the compilation.

Reports of autopsy studies in the next few years gave little evidence of improvement in this regard (e.g. D'Esopo and Marchetti 1942, Macgregor 1946, Baird et al. 1954), but some hope for slow change appeared later (Avenainen 1960, Lindgren et al. 1962, Attwood and Stewart 1968, Machin 1975). Some examples illustrate the trend. A pathology study from an Edinburgh maternity hospital noted that intracranial hemorrhage and asphyxia were three to four times more common than developmental defects in stillbirths as well as in neonatal

deaths (Agnes R. Macgregor 1946). The latter were obviously noteworthy enough to merit an account of them; they occurred in 20% of stillbirths and 10% of neonatal deaths, cardiovascular malformations were more often and more complex and severe in neonatal deaths than in stillbirths; anencephaly was common in stillbirth, spina bifida on the other hand most so in neonatal death, usually occurring in the lumbosacral region and often associated with meningocele or meyelomenigocele and hydrocephalus. This was an early recognition of the prominence later given to many aspects of what came to be called neural tube defects, with Edinburgh being in the forefront of their study.

The efforts of pathology studies to catalog the causes of stillbirths and neonatal deaths, alongside similar clinical efforts, continued unabated, largely in the usual manner. But they contributed little to furthering understanding of etiology and prevention; supporting Beard et al.'s (1954) stricture that "... classification based primarily on findings at autopsy is unsatisfactory both in theory and practice, and still more comprehensive and careful autopsies would be unlikely to solve the residual problems of aetiology and prevention." This viewpoint was disputed by Potter (1954), who wrote that it "used to be heard frequently that postmortem examinations were useless in this age period because they so rarely disclose a cause of death." But, she added sanguinely, when "an autopsy has been performed ... and an adequate clinical history is available, it is almost always possible to arrive at a probable cause of death."

Examination of postmortem series progressively fell out of favor, it seems, and fewer and fewer were made. One made not too long ago had the purpose of discovering malformation combinations in infant deaths (Evans and Polani 1980). In over eight thousand autopsies of infants who died from 1900–45 in the Hospital for Sick Children in London almost 15% had congenital malformations. Among the vast variety of defects there were 13 that were commoner, among which almost the most common were heart defects, including those in Down syndrome. It was Down syndrome, in fact, that furnished the most frequent and specific association (with heart defects, as will be fully discussed below). Categorizing these most frequent malformations, those with known genetic background were seldom accompanied by other malformations; a second group, those due to the common chromosomal aberrations, were combined with certain specific defects, but erratically; and last, those with an apparent multiplicity of causes, were frequently combined with other malformations. A discussion followed these findings, outlining the many theories that have been expounded to explain the basis of malformation association. Take your pick.

## CONGENITAL MALFORMATIONS AS CAUSES OF INFANT MORTALITY

The shifting of the pathological focus toward congenital malformations was increasingly warranted: they were to an ever greater extent the most frequent cause of death; and their diversity and multiplicity were additional challenges (e.g. Sentrakul

and Potter 1966, Sotelo-Avila and Shanklin 1967, Attwood and Stewart 1968, Valdes-Dapena and Arey 1970, Molz 1973, Usher and McLean 1974, Machin 1975).

But despite the limited statistical, demographic, and etiologic usefulness of such studies they added to the fund of knowledge. One of them contributed an interesting parenthetic finding, namely that the mortality frequency due to malformations increased between 1958 and 1970–72, while the malformation rate slightly decreased, which seemed to be largely due to the lowered anencephalus incidence, whether an outcome of temporal fluctuation or prenatal elimination was not clear (Machin 1975). Also, distinctions were noted between the causes of fetal and neonatal deaths and between deaths of various birthweights; in Winnipeg stillbirths under 2500 g had 12.2% congenital malformations and in those heavier 6.5% (Morrison and Olsen 1985), while the reverse was true in Helsinki, where the malformation frequency in neonatal deaths varied from 3% in those under 1000 g to 61% in those over 2500 g (Autio-Harmainen et al. 1983); the latter extraordinary rate undoubtedly owing to the study dealing with referral and hence biased material, a topic further discussed elsewhere, and another example of which is noted in the next paragraph.

A study from Buffalo, aside from all other matters, is a transparent example of how biases can intrude themselves; in this instance, upon the opening of a new hospital service (Terplan 1953). In comparing two consecutive periods it was found that the frequency of infant deaths from cardiovascular malformations had doubled in this time, which indeed accounted for most of the 50% overall leap in the congenital malformation level. The author himself, in the introduction to his paper, remarked that "any postmortem analysis is influenced by a considerable number of variables . . . [one being] the selection of cases for hospitalization." This indeed was the explantion for the striking increase in this malformation: In the discussion appended to the article it was noted that "an active cardiac service has developed at Buffalo Children's Hospital which attracts the more seriously ill congenital cardiacs from a considerable area," and that, in the cautious words of the writer, "the increased number of deaths . . . is due to factors other than that of increased frequency in the general population."

A distortion of a different sort may have made its appearance in a clinical and postmortem study of the causes of deaths in nearly 60,000 pregnancies gleaned from the US Collaborative Study of 1955–66 (Naeye 1979). Congenital abnormalities, said to be of major varieties, occurred in a range of frequencies in all racial groups, the highest in blacks; which makes one suspicious that minor defects may have crept into the account, one of which, a supernumerary small digit, has a relatively high frequency in this racial group, not only in the US but in Africa as well (Simpkiss and Lowe 1962, Altemus and Ferguson 1965, Warkany 1971, p. 40). Unfortunately this conjecture could not be checked since the defects were not itemized.

Decades later however pathological study failed still to pinpoint the specific cause of a large proportion of stillbirths (Morrison and Olsen 1985, Fretts et al. 1992, Settatree and Watkinson 1993, Alberman et al. 1997, Incerpi et al. 1998); although new techniques made it possible to detect chromosomal and heritable disorders in

perinatal deaths and allow rational parental counseling (Machin 1975, Anon. 1984, Faye-Peterson et al. 1999, Doyle 2000).

Reviews of the predominant and continuing position of congenital malformations among the causes of perinatal mortality have abounded in the last 20 years or so. What they recorded was a plateauing of the incidence of lethal defects at about 20% of all such deaths, with the emphasis–for seeming lack of any other course to take–on analyses of their epidemiological associations: birthweight, sex, racial, and ethnic variations, geography, sociodemography (Young and Clarke 1987, Stachenko and Battista 1987, Khoury et al. 1988, Lynberg and Khoury 1990, Guidi et al. 1991, Petrini et al. 1997, Carmichael et al. 1998, Malcoe et al. 1999). But the latest record still leaves the majority of deaths as due to perinatal conditions such as prematurity, preterm delivery, respiratory distress syndrome, and other relatively ill-defined conditions (Bell et al. 2004).

## CLASSIFICATION OF THE CAUSES OF PERINATAL MORTALITY

At this point in the consideration of perinatal mortality, its causes and their essence, it is useful to discuss classification, why classifying the causes of perinatal mortality was imperative, how it was achieved, how it changed over time, and what if any practical benefit doing this had. Identifying, and naming, different individual causes came first of course, but assembling them by commonality, i.e. organizing them into a classificatory design, objectified them and aided in comprehending them and hopefully in leading to preventive measures. The aim of such schemes as well was to set up universal categories which in toto would serve as models for wide use in study and comparison.

At first mere lists were made of individually identified causes (Holt 1915, Williams 1915). In a slight advance causes were aggregated into sets, three at first, maternal, placental, and fetal (Tingle 1926). Various other sorts of divisions were also made, of ancillary features like maternal age, birthweight, age at death, and type of delivery. After some time lists again appeared, of some length sometimes, with division into separate causes of fetal and neonatal death (Macgregor 1946, Drillien 1947). In the late 1940s and early ‘50s a different sort of list appeared, a combination of discrete factors and catalog of general groupings (e.g., Labate 1947, Allen 1948, Simpson and Geppert 1951).

And then came a classification that at one and the same time turned back the clock and turned a new leaf, advancing a system based strictly on clinical findings to explain underlying cause of perinatal death–obviously a reaction to 30 years of the failure of autopsy studies to reveal etiology, instead dwelling on immediate cause of death (Baird et al. 1954). The new system was perhaps not wholly satisfactory, but an improvement the authors believed, with the added thought that epidemiological research may be required for continued progress. The improvement it was also felt was in its objectivity and replicability.

The system, since called the Aberdeen system, reduced all causes to eight non-overlapping general groupings, none novel in itself. Putting it to the test still found

many causes to be unexplained and hence unpreventable; much of the remainder, associated with prematurity or birth trauma, perhaps preventable with improved management of labor and further understanding of the underlying disease; and fetal deformity, also quite frequent, but obviously being out of the physician's hands given short shrift. What in essence the new classification mainly offered was promise for evolving and bettered success.

This new synthesis provided a standard that has stood the test of time, and with modifications put into motion a train of similar efforts. One, soon appearing, combined the best of both worlds, integrating pathological definition and clinical association of causes, its novely being in combining many discrete causes into relatively few (Bound et al. 1956). Again however, aside from future promise, no greater potential for directed preventiveness emerged. An adaptation of this classification was used in an extremely detailed analysis of a British perinatal mortality survey (Butler and Bonham 1963, p. 186 et seq), which was further synthesized into a clinico-pathological hierarchy of perinatal death, consisting of 10 categories (Baird and Thomson 1969); by the application of which it was possible to assign cause of death to about 80% of the approximately 7000 deaths of the Perinatal Mortality Survey. A similar procedure was followed in analyzing the causes of perinatal death in the US Collaborative Study, with numerous separate disorders, many being amniotic and placental lesions, but with almost no attempt at combining for commonality (Naeye 1977).

Several minor modifications of the Aberdeen system were made during the next 25 years. A significant shift in perspective was introduced by a radically simplified system of pathological subgroupings; and also a judgment that meaningful appraisal of mortality causes cannot neglect birthweight (Wigglesworth 1980). It is apparent that this particular consideration was prompted by the growing appreciation that the major contributor to perinatal mortality was very low birthweight; but that if perinatal care was to have an impact on mortality it must concentrate its efforts on instances of moderately low birthweight. Significant also was the fact that malformation-associated death occurred evenly in all birthweights, highlighting the need for prenatal diagnosis of potentially treatable defects.

At various times since then several modified systems have been suggested. One presented a balance between the Wigglesworth minimalist scheme and the extravagantly inclusive one of Butler and Bonham, abbreviated for convenient and consistent application (Hey et al. 1986). Another redefined the Baird and Thomson categories to avoid regional and temporal differences in interpretation (Cole et al. 1986). A system devised to accommodate new knowledge and diagnostic developments advocated a more realistic causal system, called for enlarging the primary mortality categories to extend from early fetal death to perinatally related infant death (Whitefield et al. 1986). There followed an examination of the usefulness of the Wigglesworth classification by a team of individuals with backgrounds in various specialties, pathology, pediatrics, obstetrics, epidemiology (Keeling et al. 1989). Each of the specialists separately classified deaths using clinical and gross autopsy findings and various other data, and found much ambiguity and

consequently much disagreement. The effort it seems was directed at reconciling uncertainties and deciding which of the currently favored classifications is most useful for understanding and, ultimately, preventing perinatal mortality. As the authors noted, to which I add, strangely, "the topic of classification . . . is largely a British phenomenon." The Wigglesworth system has been applied in recent years in many countries in the developing world (Golding 1991), where the need to identify areas for intervention is urgent; but additional improvement seems not to be a concern, since little further along these lines has appeared in some time.

## APPLICATION OF CLASSIFYING SYSTEMS

It might have been thought that the schemes of classifying causes of perinatal death would have been put to use by comparing the rates of death due to the various causal agencies in one place or period with those in others, thus measuring success in their prevention. Several endeavors, more or less systematic, to do so were in fact made, but fewer than might have been expected.

A comparison of changes over various spans during earlier years of the century in the causes of neonatal mortality between several hospitals (Johns Hopkins 1916–20, Sloane 1909–13, Chicago Lying-in 1946–51) found that, despite problems presented by varying definition, autopsy limitation, and other matters, progress was evident for some causes, especially trauma and anoxia, but not for others; progress brought about "as a result of the improvement of conditions surrounding the pregnant patient during labor" (Potter 1954).

Changes in the Chicago hospital were compared between 1931–41 and 1961–6 (Potter 1969). Perinatal mortality of infants over 1000 g birthweight decreased 46%, the predominant reasons being amelioration of conditions associated with labor and delivery, i.e. mechanical damage resulting in trauma, and anoxia, down over 90 and 25%, respectively. The other major cause of death, congenital malformations, varied slightly but did not decrease. Nor did prematurity in fetal deaths, which brought the author to comment that "when the day comes that the premature onset of labor can be prevented, futher appreciable reductions [in perinatal mortality] can be anticipated."

Infectious disease apparently played but a small part in Chicago, but this was different elsewhere. In a Buffalo, New York hospital the greater than 20% reduction in neonatal deaths between 1935–45 and 1946–52 was due to success in combating various causes, but most significant was the reduction in infectious diseases; for one other the opposite seemed to be true, deaths due to congenital malformations increasing from 12 to 21% (Terplan 1953). This may be untrustworthy however, since some part of the increase was probably the result of the hospital being a referral center for cardiac disease. Apropos of such problems, one must be aware of the hazard of biases in the shape of malformation frequency estimation, over or under; one common type being the unappreciated effect of selection of patients, unwitting or otherwise. Especially obvious examples are given below, as well as a discussion of the topics generally.

A comparison in Birmingham, England of the basis of the nearly 20% reduction in perinatal mortality between 1945 and 1952 found most of it to be due to the decrease in the primary factors subsumed under the headings labor and postnatal complications, as well as prematurity, while other categories–complications of pregnancy and congenital malformations–had changed little or not at all (Crosse and Mackintosh 1954). By 1952 congenital malformation was responsible for 21.4% of all perinatal deaths; but the statement that the frequency in "all births" was 0.79%, being based on the number of malformed mortalities, obviously is incorrect, since not all malformations cause or are associated with death.

Studies in a teaching hospital in Helsinki enabled comparison of the immediate causes of neonatal death in 1947–9 with those in 1953–6 (Ahvenainen 1960). Even in this relatively brief time reductions occurred in trauma, infection, and possibly prematurity, but not others, especially congenital malformation, which in 1956 was responsible for 23% of the deaths. Again however this was perhaps an exaggeration, since the hospital was a referral center for all Finland.

In a survey of the causes of perinatal death in hospitals in a wide London area in 1970–3 compared with those in 1958 the largest change was in traumatic deliveries, reduced by 57%, while anoxia and malformations were somewhat increased (Machin 1975). The latter, many occurring multiply, were present in the later period in nearly one-quarter of all deaths; about two-thirds affecting the central nervous system in 1958 but only half in 1970–3, the reduction due to fewer anencephalic births, the result no doubt of prenatal diagnosis and elimination, an early example of a growing trend. "Female preponderance among malformed infants was due in part to an excess of females with neural tube defects" (a phenomenon we will return to later). A consequence of which was the relative increase in rate of deaths from cardiovascular and urogenital malformations. Two new factors made their appearance here: chromosome analysis, which enabled the discovery of abnormalities in 5.6% of analyzed specimens, including 13% of the non-neural tube lethally malformed; and the recognition of the 1.2% instances of genetic disease. The frequency of all these conditions is to be accepted cautiously however, since the mortalities were referred from other hospitals in the area and thus may in some respects be unrepresentative.

Fetal deaths decreased almost 56% in a Montreal hospital in the years between 1960 and 1989, allowing a study to be made of the changes in their causes in that period (Fretts et al. 1992). Five of the ten causes listed were significantly reduced in frequency, including isoimmunization, asphyxia, and congenital malformations, the last due predominantly if not entirely to diagnosis and termination of pregnancies with anencephaly.

A study in France of changes in the causes of neonatal mortality from 1980 to 1996 associated with the 50% decrease in their rate found that the greatest declines were in congenital malformations, anoxia, and birth trauma (Hatton et al. 2000). Relatively, however, the frequency of congenital malformations was about the same during the entire period, at about 23–27%; by far the most prevalent, almost 50% of them, were cardiovascular malformations, not those of the nervous system, hence elective abortion of neural tube defects may have been responsible for but a small

proportion of the decrease. Nevertheless 18% of lethal malformations or those presenting a risk (unspecified and unidentified) were aborted.

Comparison of changes in cause of neonatal mortality in US blacks and whites between 1980 and 1995 disclosed advances and regressions in their occurrence (Carmichael et al. 1998). The racial contrasts were especially useful in pointing to trends. As has been true for some decades, congenital malformation was the most frequent cause of neonatal death in whites, while in blacks it 'progressed' from third in 1980 to second in 1995. Also as found elsewhere, the death rate from malformations decreased in both groups during this period, largely due to prenatal elimination and neonatal surgical repair, but its frequency increased, no doubt linked to decreased mortality from other causes, especially trauma and anoxia, both of which slid far down in the list of causes.

First in this list in blacks in 1980 was preterm birth and low birthweight, which continued to be primary in 1995; while for whites they slipped from fourth to second place, increasing the black-white ratio from 3.3 to 4.6. On the contrary, the contrast between blacks and whites in rate of malformations was negligible (differing somewhat as will be seen below from the picture in postneonatal mortality).

In England and Sweden, along with overall reduction in mortality rates in the 1970s, absolute decreases occurred in the rates of many causes of death, but the main ones, malformations and anoxic conditions, increased relatively and continued to be the predominant causes of perinatal deaths (e.g. Bjerre and Östberg 1974, Alberman 1974, 1978; Karlberg et al. 1977, Edouard and Alberman 1980). More specifically, British national trends indicated that although the relative frequency of malformations remained fairly static that of prematurity had increased markedly (Edouard and Alberman 1980). In Palermo, on the contrary, the congenital malformation frequency was rather low, as might be expected of a region with a continuing high perinatal mortality rate.

In Belgium although the perinatal mortality rate had greatly decreased between 1956 and 1984 it was still high relative to other west European countries; nevertheless, taking their usual course, anoxia as a feature of perinatal mortality had greatly decreased and malformations increased (De Wals et al. 1989). The same trend was seen in Ireland, with anoxia in stillbirth not listed specifically among the most frequent causes and congenital anomalies the most common, two-thirds of the latter with neural tube defects, Ireland being a high central nervous system malformation area (Magani et al. 1990). The trend toward higher malformation rate was arrested in Montreal, deaths due to anomalies lethal at term declining in the 1970–80s, at the outset of an increasing tendency to early termination of anencephalic pregnancies (Fretts et al. 1992).

## CAUSES OF NEONATAL VERSUS POSTNEONATAL MORTALITY

This look at transitions again emphasizes the fact that a major determinant of the reduced neonatal mortality picture in the last 50 or so years of the century were advances in management of delivery with its attendant diminution in serious trauma

and respiratory conditions. The consequence of the reduction and disappearance of these and other preventable causes was the ever growing significance of the still poorly preventable ones, malformations especially. Even in China malformations have recently become a major cause of perinatal death (Dai et al. 2004).

Dominating the interests of professionals charged with understanding and preventing infant death are the causes of perinatal mortality–late fetal and early neonatal death– justifiably so since that has been and continues to be the segment of infant mortality still largely unconquered, with over half of all deaths in the first year of life occurring in the first days thereof. Deaths occurring postneonatally are no less deserving of attention, if only because of the contrasts they present with the earlier deaths and the focus they each derive thereby.

Neonatal and postneonatal mortality must be considered separately for several reasons, first because of the difference between them in the rate of their decrease over the century–the latter the greater, and thus the major basis of the infant mortality decrease as a whole; second because they are associated with largely distinct causal factors; and third because of the differences between them in the frequency and variety of their malformations.

Both the neonatal and postneonatal mortality rates in the US fell steeply throughout the century, postneonatal deaths however greatly outpacing neonatal deaths, at least till 1970; about then a slowdown began, and also a reversal, which has lasted into the earliest years of the present century (Table 1). The slowdown is better seen as changes in the proportions of infant mortality, which for postneonatal mortality plateaued at about one-third and conversely for neonatal mortality at about two-thirds (see Table 2). Nor was the US alone in this pattern since the same one or variations of it were seen in many other areas and countries surveyed (Pharoah and Morris 1979).

In the US these changes, often expressed as averages for the population as a whole, concealed important differences between its extraordinarily diverse components; in distinction e.g. to the largely homogeneous peoples of the Scandinavian countries. The largest division, until recently, is the racial one, black and white, and how these differ in this regard must be a major consideration in this work. For example, in one of these, temporal alteration in infant mortality, the pace differed for US blacks and whites: in whites the relative arrest in the decline began about 1960, but not till about 1975 for blacks.

The second reason for considering neonatal and postneonatal mortality separately are the differences between them in causation, a preliminary appreciation of which comes from examining their dissimilar associations with socioeconomic features. As noted above, this dissimilarity shows that some of these features are more and some less intrinsic to earlier and later infant mortality. Thus the near disappearance over time of the association of social differentials with neonatal death and its persistence with postneonatal death indicate that nonsocially related causes became progressively more responsible for the former and socially related ones more responsible for the latter; or put differently, that in time etiological shifts occurred and neonatal death became increasingly of prenatal origin and postneonatal death of postnatal origin.

The third difference concerns temporal changes in congenital malformation incidence. To understand this difference and to clarify the data mentioned below, the prevalence of malformations must be considered in two ways: as the level in all births (rate), and as fractions of all mortalities (frequency). As infant mortality decreased both the rate and frequency of malformations changed. Pre-1960 data are scarce, so available observations pertain to the last 40 years of the recently ended century. Malformation rate decreased in both neonatal and postneonatal mortality–slightly more in the latter–probably meaning that fewer and fewer infants died of malformations. The other possible explanation, that fewer malformed infants occurred, is ruled out by the fact that the frequency did not decrease, in either neonatal or postneonatal mortality, but instead increased significantly in the former while remaining constant in the latter (Table 3).

A racial difference should be noted: the rate declined in both whites and blacks, but more slowly in blacks, while frequency was essentially unchanged in whites but increased by nearly 50% in blacks, with the W-B malformation ratio of 2.8 in 1960 slowly decreasing to 1.5 in 2000, probably indicating diminishing nonbiological causation of mortality in blacks and consequently a growing resemblance to the white etiology picture (Table 3).

The malformation frequency in neonatal mortality increased steadily in 1960–2000 in contrast with its constancy in postneonatal mortality; nearly doubling in both races but continuing to be twice as great in whites as in blacks; with

*Table 3*. Rate (per 1000 live births) and frequency (%) of congenital malformations in postneonatal death in whites and blacks. US national data

| | Race | 1960 | 1974 | 1978 | 1988 | 2000 |
|---|---|---|---|---|---|---|
| Rate | ALL | 1.27 | 0.84 | 0.74 | 0.58 | 0.39 |
| ” | White | 1.28 | 0.82 | 0.67 | 0.55 | 0.36 |
| ” | Black | 1.33 | 1.06 | 0.83 | 0.71 | 0.60 |
| Freq | ALL | 17.4 | 18.8 | 17.2 | 15.8 | 17.3 |
| ” | White | 22.6 | 22.0 | 19.3 | 17.8 | 19.4 |
| ” | Black | 8.1 | 13.0 | 10.9 | 11.0 | 12.7 |

*Table 4*. Rate (per 1000 live births) and frequency (%) of congenital malformations in neonatal death in whites and blacks. US national data

| | Race | 1960 | 1974 | 1978 | 1988 | 2000 |
|---|---|---|---|---|---|---|
| Rate | All | 2.34 | 1.89 | 1.78 | 1.50 | 1.02 |
| ” | White | 2.45 | 1.95 | 1.83 | 1.53 | 1.01 |
| ” | Black | 1.93 | 1.88 | 1.60 | 1.49 | 1.17 |
| Freq | All | 12.5 | 15.4 | 18.8 | 23.8 | 22.1 |
| ” | White | 14.2 | 17.5 | 25.3 | 29.0 | 26.4 |
| ” | Black | 6.6 | 10.0 | 12.9 | 12.4 | 12.5 |

the frequency being inversely related to the mortality rate. The increase therefore was not due to the greater occurrence of malformations but to their resistance to prevention (more however in one race, less in the other) than were other causes of mortality.

In other words, as causes amenable to prevention abated or disappeared (predominantly infectious disease), those difficult of prevention (malformations) and newly prominent ones (mainly "disorders related to short gestation and low birthweight," i.e. preterm birth) grew in relative frequency; till in 2000 preterm birth and congenital malformation were almost tied for first place among the most frequent factors associated with neonatal death, 23.0 and 22.1% respectively. No doubt, as in time the lethality of the former is ameliorated and other causes of death are mitigated, the still obdurate malformations will further increase in relative frequency. The effects on future malformation frequency of the unsatisfactory and inefficient 'preventive' measures currently in use–prenatal surveillance and elective elimination of malformed fetuses and postnatal repair of some malformed neonates–are discussed below.

The difference between the malformation frequency patterns in neonatal and postneonatal mortality must be emphasized: while as overall mortality decreased, relative malformation frequency increased in the former, as would be expected, but not in the latter, where instead it remained steady. How can this seeming anomaly be explained? Is it due to differences between particular malformations responsible for or associated with each of the mortality segments? This will be discussed below.

## CAUSES OF POSTNEONATAL MORTALITY

Let us begin with postneonatal mortality. Despite the decrease in infant death during the century largely being due to the decrease in postneonatal death, study of the causes and associations of the latter, compared with those of neonatal mortality, is a neglected area, and relevant data regarding it are limited. One thing is clear. In western countries infectious diseases, mostly gastrointestinal and respiratory, were the major cause of postneonatal deaths in the early and middle years of the century, responsible for 50–65% of them. This waned beginning about 1960–70, and then rapidly diminished, in the US to about 13% in 1986 and then far more slowly to 12% by 1994 (Chase 1967, Khoury et al. 1984, Starfield 1985, Kleinman and Kiely 1990, Scott et al. 1998). In the US overall from about 1920 to 1978 the rate of postneonatal death associated with infection declined 99%, from 21.4 to 0.25 per 1000 live births, while that associated with malformation went down 56%, from 1.7 to 0.7, which is an indication of the relative resistance to change of the two (Starfield 1985).

Some examples depict the situation, overall and racially. In about 1960 in a southern American state about typical of most others, postneonatal death due to infectious disease far outpaced its association with congenital malformation, 48.0 vs 12.5%, with a differential thus of 3.8. The difference between whites and blacks in

this respect was striking, with differentials of 1.4 and 9.1 respectively (Siegel et al. 1966). However, while the frequency of malformations in postneonatal death was some four times greater in whites than blacks, 25 vs 6%, the rate of malformation was virtually identical, at 1.4/1000 neonatal survivors, and at the same time the rate of death from infection was six times greater in blacks, facts indicative of the relative impact of biology and environment. [Incidentally, a quite close similarity of rate of postneonatal death due to congenital malformation was also noted among various European countries (Pharoah and Morris 1978).]

Of further interest, postneonatal mortality in those with birthweights of 2500 g or less was far greater than in heavier ones, seven times greater in whites, and over twice that in blacks. This was not taken into consideration in the analysis of the causes of the deaths unfortunately. Similar birthweight findings were noted in studies of neonatal deaths in Baltimore (Shah and Abbey 1971) and California (Bendor et al. 1971), with socioeconomic factors a major determinant.

## SUDDEN INFANT DEATH SYNDROME IN POSTNEONATAL MORTALITY

An apparently new causal factor, sudden infant death syndrome (SID), not specifically named earlier, made its appearance in the 1960s, when it was said to be responsible for a negligible proportion of neonatal deaths (Khoury et al. 1984). But its previous obscurity was probably due to nebulous diagnosis (Starfield 1985), and even at present its definition remains controversial (Beckwith 2003). The trend in its recognition is illustrated by the following. It was found in a limited study in Kansas City in 1971–4 in 10% of postneonatal deaths, just behind infection at 12%, the latter already outdistanced by congenital malformations, at 59% (Kulkarni et al. 1978). It was also seen in Glasgow, by the name of ‘cot deaths,’ and was even more frequent there than congenital malformations in postperinatal mortality (Arneil et al. 1982). By the 1970s it reached new heights, at about one-third of postneonatal death, the leading cause of such deaths in the US, ahead of congenital malformations in whites, but still not as prevalent as death from infection in blacks (Khoury et al. 1984). In Canada and many European countries it was the predominant cause of death in the late 1970s and ‘80s, one and a half times more frequent than congenital malformations and many times more than infections (Semenciw et al. 1986, Kleinman and Kiely 1990).

As the contest for primacy evolved it became one between sudden infant syndrome and congenital malformation. In the 1980s the rate of death in the US from the former continued at about one-third, where it seems to have peaked, a rate almost double that of malformations in whites and three times in blacks (Iyasu et al. 1991), proportions that by and large continued to be true in the next decade (Scott et al. 1998).

Sudden infant death syndrome remains in the present century the most common cause of postneonatal death in the US, and though reduced to 23% in 2002, was still ahead of malformations at 17.7% (Anderson and Smith 2005). There

is little doubt that this reduction will continue as its causes are remedied; and malformations will be left, in all probability, as predominant as before.

## CONGENITAL MALFORMATIONS IN POSTNEONATAL MORTALITY

It is to congenital malformations therefore that attention now turns. These have long been among the foremost elements that underlie infant mortality, and are the primary focus here, foremost in intractability, foremost in perplexity. And these phenomenona have demanded ever greater attention as infant mortality declined and they became ever more prevalent as causes of these deaths (Anon. 1989). But while this inverse relationship is true of neonatal, it does not hold for postneonatal mortality. The reason for this is to be examined.

Despite becoming increasingly significant in postneonatal mortality, few writers on the problem named or described congenital malformations in detail. The few notations in earlier writings seem to have been added as afterthoughts in reports of infant mortality generally, or of neonatal mortality in particular. For example, a review of the epidemiology and medical significance of stillbirths in midcentury (Sutherland 1949) included a table listing cause of death during the postneonatal months in England and Wales, in which it was noted that the ones predominant in the neonatal period–prematurity, anoxia, etc.–were of less and less consequence in the intervals after the first month. Death from congenital malformations, on the contrary, continued to occur quite frequently, 13.9%, in the earliest of the next 3 months and then progressively diminished, to 8.5% in the next 3 months, and 6.7% in the last; but no word was given as to type of defect. Similarly, no indication of type appeared in an article particularly devoted to natal-day deaths, merely that, in Chicago in 1936–49, 19.7% of deaths in the 1st to 11th months were due to malformations (Bundesen 1953). And even in a recent report, comparing postneonatal mortality rates in Mexican mothers born in Mexico and the US, while it was noted that the frequency of malformations was almost 1.5 times greater in the former than the latter, no specifics were imparted regarding malformation type (Collins et al. 2001).

The earliest report it seems that listed specific information about malformation type in deaths at various postneonatal ages was one concerning deaths in 1954 in New York City (Wallace and Sanders 1959). Half of the deaths were due to cardiovascular malformations alone or with other conditions (as was often the case later also, the specific heart defect types were not noted); about one-quarter to central nervous system malformations, mostly spina bifida and other neural disorders, and extraordinarily (and doubtfully), one apparent instance of a very late death from anencephaly; and the rest to various urogenital and gastrointestinal malformations, etc.

In these midcentury deaths, as it was for later ones, cardiovascular and central nervous system malformations in that order predominated in postneonatal deaths. Their relative frequency was the same in postneonatal and neonatal death, the

mortality difference between them due largely to the composition of the defects; whose analysis was hindered by the scarcity even later of the naming of the defect types in postneonatal death. Especially unfortunate is the limited information about the types and individual frequencies of the cardiovascular malformations, without which the reason for these mortality differences could only be imperfectly understood. In one study in which the different anomalies were named, though the most common was ventricular septal defect, the limited number of cases was an impediment to analysis (Kulkarni et al. 1978).

It was noted in several European countries in the 1970s that as many as half of the postneonatal deaths were due to malformations, about half cardiovascular and a quarter chromosomal and central nervous system, the latter mostly spina bifida and its variants, since anencephaly is almost always lethal neonatally, when not selectively aborted (Pharoah and Morris 1979, Murphy and Botting 1989). This ranking has continued. Reports in the 1970s and ‘80s concurred in assigning to cardiovascular and nervous system defects first and second places respectively in the causal ranks (Arneil et al. 1982, Khoury et al. 1984, Semenciw et al. 1986).

In a 1980 US National Infant Mortality Surveillance, about 18% of postneonatal deaths were due to congenital malformations, second only to the rate of sudden infant death syndrome; omitting the latter raises the malformation frequency to 29%, about equal to the neonatal mortality due to malformations (Buehler et al. 1987, Berry et al. 1987). All mortality risks in blacks were about twice those in whites except for congenital malformations for which they were about equal (a fact commented on elsewere in this work). The congenital malformations in the postneonatal deaths were not detailed.

Along with the substantial decrease in the postneonatal mortality rate in 1970–80 in Massachusetts (less however than the neonatal decrease), were reductions in cardiovascular and central nervous system malformations, the former far more common however, the differential increasing from 4 to 7, no doubt indicating a far greater success in preventing the latter than in surgically dealing with the former (Stachenko and Battista 1987).

These rankings persisted into the 1990s. Seen best by omitting sudden infant syndrome deaths, the most frequent cause of postneonatal death was cardiovascular malformation with central nervous malformation a distant second, the differential increasing from about 3.6 in 1980 to about 4.8 in 1994 (Scott et al. 1998). The frequency of malformation-associated death was appreciable, about 29% in whites and 16% in blacks, the rates down in this period 2.6% in whites and 1.2% in blacks– the greater improvement in the former probably the result of increased prenatal selection and improved neonatal survival after surgery.

This is apparently where the matter rests with regard to the significant causes of postneonatal mortality at the outset of the 21st century. What does the future hold? As the remaining infectious diseases (especially respiratory) are further mitigated, and as sudden infant death syndrome further abates, congenital malformation, the prevalent major biological cause of death, will continue it seems from present projections its upward pace; to be reversed only–until the ideal solution, prevention ‘ab

ovo,' is attained–through avoidance by provisional measures: increasingly refined means of prenatal elimination and surgical correction. (The preventive effect of folic acid, as yet not definitely substantiated, will be discussed below.)

## CONGENITAL MALFORMATIONS IN PERINATAL MORTALITY

As the rate of infant mortality continually decreased during the course of the 20th century the fraction of deaths associated with congenital malformations continually increased. In the US e.g. it was 5% in the first decade and rose to 22% toward its end (Warkany 1971, p 42, Anon. 1999). Till recently this record changed little–even in midcentury World Health Organization population statistics noted that something like one-third of all deaths from malformations occurred in the neonatal period, almost half in the first month, and 80% in the first year (Lamy and Frézal 1961)–but it now seems to have reached a plateau and may even be decreasing. In 2002 it was 20.1% in infant deaths and 24.2% in neonatal deaths, making this the first in rank of all causes of infant death (Anderson and Smith 2005). All this happened of course because congenital malformation births have continued to be far less preventable than other causes of infant death. This was substantiated by a mid-century analysis that found that in 1960–80 there was 54% decline in infant mortality due to all causes, while that due to congenital malformations declined far less, by 31% (Berry et al. 1987).

This decreased infant mortality, however, chiefly benefited the postneonatal months, thus leaving a progressively greater fraction of deaths to occur in the first weeks of life; till in 2000 in the US two-thirds of infant deaths took place in the first 4 weeks and 40% on the 1st day of life alone (http://www3.who.int/whosis/mort/table2_ process.cfm). Despite this trend detailed information about changes over time in the frequency of particular malformations in these deaths is relatively limited. Thus while there was knowledge at the end of the 20th century of the frequency of malformations in neonatal death (36% in 1st-day deaths, and 54% and 17% respectively in early and late neonatal deaths), facts are scarce documenting the progressive change that may have occurred over time in individual malformation types in these segments of neonatal death. This ignorance is added to by the ethnic, racial, and geographic variations in the prevalence of many of the most common of the malformations, all to be discussed below.

## THE TERM 'PERINATAL MORTALITY'

That these earliest subdivisions of infant mortality have special significance has long been recognized. It was Sigmund Peller who, soon after the war to end all wars, first noted that "stillbirths and deaths which occur within a few days after birth have in common a complex of causes which differ from the pattern in older infants," and suggested for this unit the term perinatal mortality (Peller 1923, 1965). As later spelled out, what separates perinatal from postperinatal death is that most of the causes of the former originate prenatally while most of those of the latter originate

postnatally. Peller assumed that this difference would weaken as the pattern of causes of early death changed, e.g. through conquest of infectious diseases and death of infants usually dying of causes of prenatal origin delayed to later weeks.

Despite the shared origin of the causes of perinatal mortality their segments differ in frequency and type of malformation. Each of them, stillbirth and early neonatal mortality, must therefore be considered individually, to make it possible to chart the changes in the prevalence of the malformations distinctive of each of them. This is a worthy effort. It shall be seen how well it can be accomplished.

Many accounts, pathologic, pediatric, obstetric, and epidemiologic, of the proximate causes of death in these earliest phases of life included information about malformations, some cursorily, some in detail. Many clinical reports mentioned congenital defects and sometimes listed them in perinatal deaths but not always in its segments separately. Even those however that did not restrict their findings to perinatal deaths or did not present the defects according to the segment they occurred in are to be considered for whatever relevant information it may have been possible to extract from them.

The bounds of this inquiry are limited to the malformations occurring most frequently by far in perinatal mortality, those of the cardiovascular and central nervous systems, and thus it is on the voluminous literature concerned with these defects, here and in further sections below, that the following summary will be focused.

Mortality in the perinatal period has been a major concern of individuals in many spheres of life in the 20th century–medical, social and public health, lay groups, and others. It is obstetricians in particular, care givers who had as their province the responsibility of understanding and preventing these deaths, from whose pens reports of them and their causes at first principally emanated. And because the proportion of all infant deaths they comprised increased with time and because of the inherent complexities of their gravest causes, more and more dominated by congenital malformations, perinatal deaths demanded and received the greatest attention.

## EARLY US STUDIES

Perhaps the earliest example of the concern with perinatal deaths was the dismay expressed by the then Professor of Obstetrics at Johns Hopkins University, J. Whitridge Williams (1915) at the “inexcusably poor” obstetric care at the time in the US. In a presidential address to the American Association for the Study and Prevention of Infant Mortality, entitled “The limitations and possibilities of prenatal care,” he outlined what the ideal organization of an obstetric hospital should be.

And in the same address he also described the causes of “fetal death” in 10,000 consecutive births in the Johns Hopkins Hospital in Baltimore. It is this description that this section begins with, because it inaugurates and in many ways exemplifies the patterns in subsequent such reports. By fetal death, as was customary of the

time, was meant late fetal death plus death in the first 2 weeks after birth, the latter so defined no doubt because postpartum women usually stayed in hospital that long in that more leisurely and unpressured era.

As was then usually the case, most of the deaths were autopsied, and a relatively small proportion, 3.4%, trustworthily found to have deformities "incompatible with life." Remarkably taken note of at that early time was the striking racial difference in frequency of fatal deformities, 6.6% in whites, 1.4% in blacks. [It was not till years later that this discrepancy was again taken note of (Wolff 1944)]. And differing also from many later reports, the malformations were named; and although not assigned to the early mortality segments, deductions regarding this point can be made. More than half of the defects were of the central nervous system, and of these about half were "acrania," i.e. anencephaly; no doubt most of which occurred in stillbirths since virtually all anencephalics are dead at or soon after birth. The remainder comprised defects of many parts and types, but of the heart none was mentioned, no doubt a further indication that stillbirths were the main subject, since later work has shown cardiovascular malformations to be relatively little present in fetal deaths.

There was little hope of preventing such conditions, Williams realized, since as he perceptively commented they "originated during the first weeks of pregnancy, and therefore no diminution in the number of deaths from this cause can be expected from prenatal care." The latter being his primary responsibility, he gave the malformations scant attention.

Nor generally did other early and later writers give malformations much more than a passing glance, reporting them in toto if at all, and seldom communicating the segments of early death in which they occurred. An exception to this was made by L. Emmett Holt and Ellen C. Babbitt (1915), also in an address at the aforementioned Boston meeting. They presented their findings in 10,000 consecutive births (a good round number conveniently stopped at) in the Sloane Hospital for Women in New York City, in the 6 or so years ending 1913, recording malformations in stillbirths and neonatal deaths separately in some detail. In the former were noted "monsters," anencephaly of course, but not their frequency nor other malformations, if any; and 2.8 and 3.9% malformations in 1st-day and 1st-week deaths respectively, but only named were four instances of cardiovascular (1.4%) and two central nervous system defects.

The very low frequency of malformations in the deaths reported in these two publications, and others in the earlier years of the century (e.g. McQuarrie 1919), was of course due to their being overshadowed by the vast predominence at the time of numerous other causal factors, discussed above. The same was still true some years later in certain localities. In large hospitals, in births extending over many years, low frequencies of congenital defects were seen, in Baltimore in stillbirths 16/1000, including a spina bifida (Dippel 1934), and in Boston 1.6/1000 neonatal mortalities, of which 46% were unnamed cardiovascular malformations (Clifford 1936). In other regions a shift happened rather soon, as evidenced by the leap in malformation frequency in mortalities. For example, comparison of earlier and later

Chicago hospital records showed that malformations increased from about 3% in the years before and just after the first world war to about 19% in the years following the second world war (Potter 1954) and to 29% in the 10–15 years thereafter (Potter and Davis 1969); the large increase no doubt explained by the marked fall in infant mortality in the interval surveyed.

A series of detailed reports from Chicago, which continued over several decades (Potter and Adair 1943), began with noting a malformation frequency of 14.9% in early neonatal mortality, the great majority in 1st-day deaths; cardiovascular malformations, again unnamed, were found in 4.1%, but the only mention of central nervous system defects was to "11 monsters (6 hydrocephalus and 5 anencephalus);" but the reference is vague, if it is taken to mean that these 11 occurred in the 225 stillbirths, as is likely, this would give the latter a malformation frequency of 4.9% and reduce that in the neonatal mortalities to 9.2%, a bit more realistic for the time (Swanson et al. 1936). A further important piece of information imparted was that the malformation frequency was over three times as great in full term as in premature offspring (26.4 vs 8.1%). Unfortunately the malformation type in these two classes was not divulged, but the smaller frequency in the latter no doubt means that many of them died principally of conditions related to prematurity. Additional information about specific malformations in immediately succeeding communications from Chicago was sparse; one noted 4.7% central nervous system and 2.0% cardiovascular malformations in stillbirths and neonatal deaths combined.

Resuming the initial practice, two studies recorded malformations separately in the individual segments of infant mortality in births in the 1940s (Simpson and Geppert 1951, Hofmeister and Paegel 1952). Those of the central nervous system predominated in stillbirths (9.1% in one study, 12.6% in the other) and were also present in neonatal deaths, but differed in composition, anencephaly almost exclusively in the former and meningocele only in the latter; cardiovascular malformations (7.9%) were seen in the latter also, but in one study only and strangely absent in the other. Hydrocephalus was noted in neonatal deaths in both studies. It must be remembered, though not explicitly mentioned, that hydrocephalus and spina bifida are often associated.

Explicit information of relevance here was obtained from death certificate records from New York City for 1954 (Wallace and Sanders 1959). They showed that in deaths under 1 day of age (probably meaning stillbirths) 26% had anencephaly and 6% spina bifida, alone or with other neural defects; and that in neonatal deaths 4% had anencephaly and 8% spina bifida, an apparently unusual instance of anencephalics surviving to die neonatally. Respecting cardiovascular malformations (not including Down syndrome), 7% were in stillbirths and 38% died neonatally.

## BRITISH AND IRISH STUDIES

The first inquiry generally into the causes of fetal death in this part of the world apparently was a 1914 survey of 300 fetal deaths in London hospitals and other institutions (cited by Macfarlane 1984). The earliest full report is an account from

the Liverpool Maternity Hospital of births in 1923–32 (Malpas 1937). Though not explicit, evidence presented clearly pointed to the fact that many perhaps most of the infant deaths reported were stillbirths and neonatal deaths, since over half of them were associated with central nervous system malformations (16% anencephaly, 13% spina bifida, plus the usually rare defect iniencephaly, and hydrocephalus). The prevalence of the first, 3.2/1000 births, is almost identical with the one found 27 years later (Smithells et al. 1964), indicating its constancy during this extended period. Cardiovascular malformations, though relatively few, at 3.4%, were among the next most frequent malformations in mortalities, some of which probably occurred in the early deaths, but this is not clear since age at death was not stated. An interesting observation was that abortions were twice as frequent in fraternities in which an anencephalus occurred as in those in which it did not occur, a clue to etiology not followed up for many years.

Malpas' insights into problems still faced today are extraordinary and should not be forgotten. He wrote: "For a variety of reasons the problems of human teratogenesis cannot be investigated except by indirect methods. The techniques of experimental embryology are not available, a majority of foetal malformations lead to stillbirth or neonatal death, so that direct pedigrees can rarely be obtained; finally in the case of monstrous births the search for significant aetiological factors is usually fruitless. From the standpoint of the inquirer the parents of malformed children generally appear disconcertingly normal. Correlation between the incidence of malformations and the incidence of various factors or qualities of the parental stock is almost the only possible method of investigation." Not bad for 70 years ago.

A brief account was given of malformations in neonatal deaths occurring in 1939–42 in the Belfast Royal Maternity Hospital (Allen 1948). Central nervous system malformations (spina bifida and meningocele; not surprisingly, no anencephaly) were present in almost half of them. The great prevalence of neural defects (3.2/1000 births) was part of their high rate in Ireland, as will be discussed in detail in the second volume. Among the next most common (3.8%) were cardiovascular malformations (which included ventricular septal defect, patent foramen ovale, coarctation of aorta). The overall frequency of malformations, 20%, was far greater in mature than immature births (i.e. under 5.5 lb): 40 vs 11%; 24% in the latter when deaths attributed to immaturity are omitted.

In Birmingham, between 1945 and 1952, while the rate of stillbirth and neonatal mortality was reduced in each about equally, by about 12%, the congenital malformation frequency increased disproportionately, by 36 and 59% respectively, which may be traced to the frequency of immaturity in neonates having been halved (Crosse and Macintosh 1954). The defects in each segment were listed separately only in a special investigation in 1948–9, when it was recorded that over 90% of malformed stillbirths had central nervous system malformations but no cardiovascular ones, and 19% of malformed neonatal deaths central nervous system and 23% cardiovascular defects, none named.

Data regarding congenital malformations in stillbirths and infant deaths in 1938–55 in the Aberdeen Maternity Hospital were presented jointly (Anderson

et al. 1958). Most of the distinction between the segments can be inferred however. In all likelihood virtually all the 25% of the malformed that were anencephalic were stillborn, and most of the 37% with other malformations of the central nervous system, which included hydrocephalus and spina bifida, no doubt occurred in neonatal deaths. Other malformations, comprising 38%, undoubtedly included cardiovascular ones, were were not explicitly mentioned. The lower rate of anencephaly in Aberdeen, 1.6/1000 births, than the national one in Scotland in stillbirths alone, 2.7/1000, is probably attributable to geographic variation.

In an autopsy study in London of stillbirths and neonatal deaths during 1948–55, congenital malformations were found in 13% of the former and 15% of the latter; in all 5% had hydrocephalus plus meningocele, 2% anencephaly, and 2% cardiovascular defects, with no indication in which segment they occurred (Bound et al. 1956). The hospital anencephaly rate was 0.9/1000 births, which is significantly lower than the 1.4/1000 births recorded in greater London in 1965–8 (Carter and Evans 1973). It is not clear what accounted for this shortage.

In pregnancies in 1957 in Belfast 90% of the congenitally malformed stillbirths had anencephaly alone or with related neural abnormalities (spina bifida, etc.) and 6% cardiovascular defects; in the malformed early neonatal deaths 17% had anencephaly (almost all dying soon after birth), 23% spina bifida, and 17% cardiovascular defects (without Down syndrome); 69% of the anencephalics were female (Stevenson and Warnock 1959). In all births the rate of neural tube anomalies was 8.3/1000 total births, of which 6.8/1000 were anencephalics, an extraordinarily high rate, among the highest ever recorded, compared with any other, e.g. with the one noted just above for London.

An influential survey of British births in March-May 1958, though wide ranging, failed to provide complete information regarding causes of death in individual segments of perinatal mortality, noting only that 3.4% of the births were perinatal deaths, of which about two-thirds were stillbirths, and that 24% of the total were malformed, with equal proportions in each (Butler and Bonham 1963).

The survey however presented a detailed analysis of death occurring in Britain in a 1-week period in March (the ‘control week’). In these births the total perinatal malformation rate was 17.5/1000 total births, which was contrasted with 11.2 in Sweden and 12.2 in Japan. The anencephaly rate was 1.8/1000 births (all dead at birth), 3.3 for spina bifida, and 1.1 for all other neural defects, for a total for of 6.2/1000. Thus central nervous system malformation was present in over one-third of all perinatal deaths, over 82% of which were anencephaly and spina bifida. The rate of cardiovascular malformations was 6.4/1000 in utero at 28 weeks, 5.9 in livebirths, 5.4 in early, and 5.1 in late neonatal death. These were of several varieties, two-thirds multiple, the majority surgically incorrectable.

The second part of the survey gave revised information regarding congenital malformations in singleton mortalities, but not in stillbirth and early neonatal death separately (Butler and Alberman 1969). Over half of the malformed perinatal deaths had some form of neural defect, about 30% anencephaly, 16% spina bifida, and 10% all others. Cardiovascular malformations of a wide variety occurred in 13%

of perinatal deaths, the commonest of which, comprising more than half, were ventricular septal defect, left heart hypoplasia, coarctation, and pulmonary valve stenosis/hypoplasia. The lethal ones, it was deduced, were about one fifth of all cardiovascular defects.

In a survey in England and Wales in 1961–6 of malformed stillbirths, 88% had defects of the central nervous system, vastly outnumbering all others, almost two-thirds anencephaly (as usual, females were in great excess), with a rate of 1.8/1000 births, 17% hydrocephalus (association with other defects unclear), and 12% spina bifida; another 2.2% were cardiovascular, no doubt of the most severe types (Rogers 1969). Neonatal deaths were not mentioned. A historical survey of infant deaths associated with congenital malformations of the central nervous and cardiovascular systems made from the Registrar General's Annual Reviews from 1848 to 1967 suggested that at times epidemics of these conditions had occurred (Rogers and Morris 1969).

A survey of malformations in all births in South Wales in 1964–6 (Richards and Lowe 1971) was followed up by a study of congenital malformations in fetal and infant mortality, not explicitly noted by perinatal segment however, though inferences once more can be made (Richards 1973). Half of all mortalities had malformations of the central nervous and cardiovascular systems (33% the former, 18% the latter). Over 90% of the anencephalics were stillborn, but extraordinarily, a small number survived to die within 4 days of birth; 22% of the spina bifidas were stillborn, 16% of liveborn spina bifidas without anencephaly died by 1 week, and 59% by 1 year of birth. Of those with cardiovascular malformations, including malformed Down syndrome, 2% were stillborn, 17% died in the 1st week, and 28% postperinatally. Many types of heart defect were named, mortality by 1 year ranging from 41% for septal defects to 100% for coarctation of the aorta.

A British survey in 1970 found that 20% of perinatal mortalities were due to major congenital malformations, up from 15% 12 years earlier, accounting in both for about 5/1000 deliveries (Claireaux 1973). In the most recent year half of the deaths were due to central nervous system and half to cardiovascular system defects. Most valuably, the rates of numerous specific cardiovascular system defects were noted, e.g. 4/1000 births for bicuspid aortic valves, seldom recognized in infancy, etc.; with the observation that mortality rates for these conditions were almost the reverse of their frequencies, e.g. very high, 90%, for transposition and truncus arteriosus, and relatively low, 23%, for patent ductus arteriosus.

In a perinatal mortality survey in 1977 in Scotland 14% of analyzed singletons had central nervous system and 4% cardiovascular malformations; malformation types were not named and defects in the segments not detailed (McIlwaine et al. 1979).

Studies in Leicestershire in 1976–85 of the genetic basis of congenital malformations other than those of the neural tube, found in perinatal deaths a low frequency of cardiovascular malformations, about 3%, or about 0.38/1000 births; but most pertinently, that two-thirds of the abnormalities had a genetic contribution and that the greater rate of lethal malformations in the Asian than white population seemed

to be due to the greater occurrence of certain autosomal recessive disorders in the former (Young et al. 1986, Young and Clarke 1987).

An analysis of the causes of stillbirth and neonatal death in 1979–81 in England and Wales, as learned from a large sample of death certificates, supported the distinction between defects predominant in each of the perinatal partitions (Murphy and Botting 1989). Malformations of the central nervous system occurred in 17% of the stillbirths and 14% of the neonatal deaths; but the composition of defects in them was different, 48% of the defects in the former being anencephalus and 9% in the latter, while spina bifida was 22% in the former and 49% in the latter. A marked and major difference, even more so than of those of the central nervous system, involved cardiovascular defects, being 1.2% in stillbirth and 16% in neonatal mortality.

It is of importance to note the effect on phenomena of interest here of selective pregnancy termination: in the North-West Thames Region in a 10-year period at least half of the fall in the perinatal mortality rate was attributable to pregnancy terminations for malformations, in 1990–1 alone neural tube defects accounted for 35% of terminations performed for specific conditions (Wigglesworth 1994).

In a university hospital in Galway, Ireland in 1972–82 the stillbirth rate was 12/1000 births. One-fifth were malformed, 3% with cardiovascular malformations, 79% with central nervous system defects, two-thirds of the neural tube, for a rate of 1.62/1000 births, relatively low for Ireland (Magani et al. 1990). The widely noted decreased rate of neural tube defect was not seen in this period in this hospital, the pattern of occurrence remaining without change. The quite low incidence and the lack of change were not commented on, but of course stemed from the abortion policy in that country.

## LATER US AND CANADA STUDIES

The vast US Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke included a detailed study of the numerous stillbirths and neonatal deaths in over 43,000 randomly selected consecutive single births in 1959–64 (Froehlich and Fujikura 1969). Congenital malformations of the central nervous system were present in 3.1% of stillbirths (1.8 and 4.6% in males and females respectively, the disparity due to great excess, 89%, of females with anencephaly and spina bifida) and in 2.5% of neonatal deaths (with a much smaller difference between the sexes, 2.2 and 2.8% in males and females). Defects of the cardiovascular system were noted in 4% of stillbirths and 8% of neonatal deaths (equally in both sexes in both segments), including at least 14 different types, the commonest ventricular septal defect at 1.6% in stillbirths and 3.6% in neonatal deaths.

The difference between the sexes (and between whites and blacks–six times larger in whites, at 1.25/1000, than in blacks, at 0.19/1000, eight times larger in white than black females)–in the frequency of anencephaly in stillbirths, but hardly any in neonatal deaths is striking and merits discussion. On the whole, there was

a deficiency of anencephaly and spina bifida, with a combined rate of 0.88/1000 births, significantly below the nationwide prevalence in 1970 of 1.3/1000 births (Yen et al. 1992). This was no doubt due to the large proportion of black pregnancies (52%) among the participants in the study.

A follow-up pathology study was made of the underlying causes of perinatal mortality in the Collaborative Study (Naeye 1977). In part this may have been an improvement, since neonatal death was divided into early and late, but the frequency of congenital malformations found was low: in 6% of stillbirths, 11% of early neonatal deaths, and 29% of late neonatal deaths; in addition the types of defects were not specified.

A study of malformations in neonatal deaths in 1978–80 in Alabama took the innovative step of relating weight to particular malformation types, finding that it was not always direct, with that of neural tube defects being inverse, ranging from 37% in the low weight group, 18% in the intermediate one, to 10% in the high weight group, while for cardiovascular malformations it was the reverse, going from 0% to 64% (Goldenberg et al. 1983).

The frequency of congenital malformations in neonatal mortality in Massachusetts increased from 14.8 to 20.5% in the years 1970–80; but of the types noted only cardiovascular defects decreased, by 14%, while those of the central nervous system were unchanged, at about 11%, and chromosomal defects tripled–the last most unlikely, causing doubt of the interpretation of the death certificate gleanings (Stachenko 1987). As others have noted (e.g. Morrison and Olsen 1985), the frequency of malformations was significantly greater in those under than over 2500 g, but the specific defects in the weight groups was not recorded.

A comparison of infant mortality from congenital malformations in selected European countries and the US for the years 1976–85 noted a great decline in death due to anencephaly, undoubtedly due to prenatal elimination, and hence its virtual disappearance as a cause of death in Europe, but less so in the US; with a consequent increase in proportion of deaths due to cardiovascular malformations, despite the decline in the frequency of mortality from the latter, to about 38–40% (Powell-Griner and Woolbright 1990).

In stillbirths in a Montreal hospital in 1961–88 lethal malformations declined from 1.1 to 0.54/1000 births largely because of early termination of anencephalic pregnancies; deaths from other malformations also declined, but were not detailed (Fretts et al. 1992).

A US national program monitoring frequency at birth of selected congenital malformations using hospital discharge data found that in 1979–89 anencephaly and spina bifida declined 6.4 and 3.4% per year respectively, while various cardiovascular malformations significantly increased by as much as 22% (Edmonds and James 1993).

In a study of autopsies in hospitals in Rhode Island in 1958–95 8.8% of stillbirths and neonates had malformations of the central nervous system, almost half with neural tube defects, but the malformation types in each were not reported individually (Pinar et al. 1998). The only clue as to such details was the finding

that in stillbirths the sex ratio was more heavily female while in neonates it was the reverse, indicating that anencephaly predominated in the former and other defects in the latter.

Infant mortality in New York City declined from 13.3/1000 live births in 1989 to 10.2/1000 in 1992, much of the decline attributed to the decreased malformation rate of nearly 11%, as well as to the lowered mortality rate of low birthweight infants (Kalter et al. 1998).

The US infant mortality rate attributable to congenital malformations declined 35% in 1980–95 to 1.7/1000 births, as deaths associated with many types of malformations decreased, but the proportion of infant deaths due to malformations rose 10% to 22.2% (Petrini et al. 1998). By 1995, discounting chromosomal defects, the two most common malformation types were those of the cardiovascular and central nervous systems, at 35 and 13% of all respectively, although the frequencies of both had declined substantially. The decrease of cardiovascular malformations resulted in part from postnatal repair, e.g. of hypoplastic left heart, transposition, etc., but mostly by far from a 61% decrease in ventricular septal defects, no doubt a diagnostic reaction to an earlier reported increase in this condition so great it had been labeled an 'epidemic' (Layde et al. 1980).

[Parenthetically, it now seems clear that the so-called epidemic was due to the detection of small, isolated septal defects of the sorts largely overlooked by past less precise methods of diagnosis, most of which, incidentally, close spontaneously by 1 year of age and have no physiological consequence (Martin et al. 1989, Fixler et al. 1989, Meberg et al. 1994). For further details see below.]

As for central nervous system malformations, their reduction was due mostly to the decrease in anencephalus and its concomitants, probably the result of continuation of the temporal trend (see below) and selective prenatal elimination. This study unfortunately gave no details regarding defects in the earliest compartments of perinatal mortality. An etiological category that saw an increase in reported prevalence were chromosomal aberrations, especially trisomies 18 and 13, which grew 36%. Obviously these were not novel occurrences, but discoveries attendant upon new techniques and new focuses, particularly in the unborn, and thus refer almost exclusively to the perinatal period.

A study of changes in malformation-specific infant mortality in 1981–95 in all but three provinces of Canada are of interest (Wen et al. 2000). Although the infant mortality rate declined substantially, the frequency of infant deaths from malformations remained essentially unchanged, at 30–34% during the period. The authors were apparently puzzled by this seeming contradiction, failing to appreciate that the great reduction in infant mortality generally in Canada had till then led perhaps to as yet further irreducible levels, making for the constancy in the malformation frequency. During this period the rate of anencephaly plus spina bifida decreased 67%, and of cardiovascular malformations 30%, these substantial reductions being largely attributed to increased prenatal diagnosis and termination of affected pregnancies and to improved surgical procedures.

A further report from Canada attempted to refine these findings by examining changes in 1985–96 in malformation prevalence in stillbirths and infant deaths according to gestational age (Liu et al. 2001). In the very youngest fetuses, of about 25 weeks and less, the malformation-related death rate increased, while in older ones it decreased, the difference, according to the authors, probably due to many more terminations of earlier than more advanced pregnancies. This interpretation is belied to some extent by the fact that, as regards particular malformations, the death rate from anencephaly decreased a mere 8% in the youngest fetuses, while in older ones and in infants it decreased 65 and 56% respectively. The death rate from spina bifida on the contrary increased in the youngest fetuses, though relatively small numbers make this uncertain, but decreased in the others. The pattern for cardiovascular malformations was rather different, death from which increasing markedly in the youngest fetuses, and decreasing moderately in older ones and infants. These differences would have been made explicit and concrete if it had been possible to present early neonatal in addition to fetal data.

A further analysis of the data found that the decline in the rate of malformation-associated mortality was mostly due to selective abortion of malformed fetuses (Liu et al. 2002a,b). This was predominantly so in the youngest gestational ages, since it was in these that the termination rate was greatest, while in older offspring it decreased. The conspicuous, unexplained, exception was that deaths of anencephalic young fetuses decreased, implying–but it seems difficult to accept–that diagnosis of this condition in younger fetuses is more difficult than in older ones. The rate of death from cardiovascular malformations was also greatly reduced, in older, but not younger, fetuses and infants, again mostly through reduction in ventricular septal defects, for which see above probable explanation.

A similar analysis of malformation-specific infant mortality was conducted in the US using 1970–97 data (Lee et al. 2001). Again, as overall infant mortality decreased in these years, the proportion due to congenital malformations progressively increased, reaching 22.1% in 1997. [The considerable difference between the latter and the 35% in Canada reported by Wen et al. (2000) demands explanation. The infant mortality decrease in Canada and the US in this period were similar; the assortment of major malformations enumerated was similar; and there is no reason to believe that ascertainment success differed.

A significant overall decline was noted in the rate of lethal malformations in the period surveyed, as to one extent or another were those of specific malformations. Thus death from central nervous system malformations declined 64% (53% in 1970–90 alone; why the latter is especially important will be discussed below), and from cardiovascular malformations about 50%. A detailed account was given of the numerous types of the latter, seventeen in all, the most frequent of which was hypoplastic left heart syndrome, forming about one-fifth of them, decreasing 20%, mostly in 1985–97. The great improvment in the frequency of cardiovascular malformations especially remains to be explained. That of various chromosomal disorders, not surprisingly, appeared to be fairly constant in rate, even while the most prevalent of them, trisomy 13, declined 8% in 1985–97.

An international survey of the relation of congenital anomalies and infant mortality found continuous declines since 1950 in many countries worldwide in the rate of infant mortality attributable to congenital malformations, including spina bifida and cardiovascular malformations; with the proportion of all infant deaths attributable to malformations, in the 1990s, ranging from 35–40% in Scandinavia, to 20% in South America (Rosano et al. 2000).

## STUDIES ELSEWHERE

A questionaire survey of births in Finnish maternity hospitals in 1957–8 found that nearly three-quarters of perinatal mortalities were malformed (Timonen et al. 1968). Just over one-quarter of them had central nervous system malformations; while the frequency of cardiovascular malformations was masked by their being reported together with others; the population rates were 5.6 and 1.2/1000 births respectively. The defects in the perinatal mortality segments were not listed separately.

A pathology study of perinatal deaths in Düsseldorf and Zürich in 1957–70 found congenital malformations in 9% of stillbirths and 31% of neonatal deaths (Molz 1973). Over half of the former and 15% of the latter had central nervous system defects, and 0.8% of the former and 41% of the latter had cardiovascular malformations.

The causes of infant death were compared in Göteborg and Palermo and malformations found in 27 and 4% of early neonatal deaths respectively in these two European areas, the contrast obviously a reflection of the threefold difference in the overall mortality rate in those two countries (Karlberg et al. 1977). The composition of the defects was not noted however, a pity since that may have further explained the difference.

National inquiries in France in 1972 and 1975–6 regarding perinatal mortality pathology established that the rates of most malformations during that period had remained fairly stable, e.g. central nervous system malformations were about 1.3–1.4/1000 births, that of cardiovascular defects had apparently decreased, from 1.3 to 1.1/1000, and most others had also varied little, yet the overall rate of death from malformation had increased an amazing 43% (Rumeau-Rouquette et al. 1978). The reason was an exceedingly zealous recorder of the usually minor defect clubfoot, and hence as the authors note, "imputable très vraisemblablement à la qualité de l'examen." Other examples of such 'special situations' are discussed elsewhere in the text.

A study of perinatal mortality in Belgium found 22% of stillbirths and 39% of early neonatal deaths due to congenital malformations, the types however not specified (De Wals et al. 1989).

National French statistics were used to chart changes in the causes of infant mortality in 1980–96 (Hatton et al. 2000). The rate of central nervous system and cardiovascular malformations in neonatal death, as they have elsewhere, declined, 48 and 41%, while remaining stable in frequency, at 2–3 and 11–12%, respectively. The latter figures are unhelpful however, since they conflate heterogeneous early and late neonatal data.

To what the widespread longterm decrease in mortality due to cardiovascular malformations, as seen e.g. in an international survey (Rosano et al. 2000), may be attributed is more difficult to say. This is discussed fully below.

## SUMMARY AND DISCUSSION

In sum, the above tedious repetition overwhelmingly declares that death resulting from the malformations that are the focus of this work–those of the cardiovascular systems in this volume, those of the central nervous system in a subsequent volume–are principally associated with specific times of early life: failure of the anterior neural tube to close in embryonic life, causing what is called anencephaly, is in effect always lethal at birth or by early neonatal life, while malclosure of the posterior neural tube, spina bifida, being a less severe defect and interfering less with viability, causes death, when it does so, later in infancy. (Incidentally, one may ask why in the face of its gross deviation from normality, anencephaly rarely causes death in embryonic or early fetal life.)

With regard to the central nervous system defects, it appears from the reports reviewed above that the decrease in the rate of infant death due to them was not the result of their being prevented, by any therapeutic measure, but partly, in more recent years, to termination of affected pregnancies by selective abortion; and hence that the 'load' of these defects, i.e. their frequency 'ab ovo' was not lessened (Edmonds and James 1993, Liu et al. 2002b). The sole other factor to which the decrement can be attributed, in the years prior to dietary supplementation, is the continuation of the historic downward trend that had been occurring widely for years (Naggan 1969, Windham and Edmonds 1982, Stein et al. 1982, Mathers and Field 1983, Romijn and Treffers 1983, Källén and Löfkvist 1984, Lorber and Ward 1985, Laurence 1989, Yen et al. 1992, Rosano et al. 2000). This situation requires much discussion, which will come in the next volume.

Cardiovascular malformations, in distinction, are found relatively infrequently in late fetal death (perhaps–though this is unproven–because many are present in early embryonic deaths). They are in fact far more prevalent in neonatal death than in stillbirths, more at that time than are neural defects. It is these abnormalities, in fact, that are the commonest in toto of all congenital malformations, and so it is with them that the quest for their nature and causes commences.

Summarizing and making the findings outlined above concrete was a 5-decade literature search into the relation of malformation and perinatal mortality and the long-term trends in both (Kalter 1991). Made in pre-computer days, this super review examined 263 otherwise unanalyzed hospital-based and other European and American (US and Canada) medical articles published in 1940–88; from which it drew in some detail the picture of malformations found in stillbirth and early neonatal mortality.

From this multitude of data it was found that as the rate of perinatal death fell, about 70–80% in both regions, chiefly in the last half of the period, with stillbirths and early neonatal deaths falling comparably, not surprisingly the frequency of

congenital malformations rose concurrently; but to a far greater degree in early neonatal deaths than in stillbirths, so that in the 1980s it was 2–3 greater in the latter than in the former.

Various considerations, especially related to birthweight, led to the deduction that the distribution of malformations in stillbirths and neonatal deaths would be quite different from eachother. And this was the case: in stillbirths the predominant specific defects (75–85%) were those of the central nervous system, mostly failure of neural tube closure, mainly anencephaly, with no other category even reaching 10%; whereas in neonatal death the commonest defects (38–40%) were those of the cardiovascular system, with central nervous system defects not far behind, at 28%, but in this case mainly spina bifida. Facts regarding the specific defects were largely inferred, since the original sources did not always specify them, especially in stillbirth and neonatal death separately. Now on to the matter of cardiovascular malformations.

CHAPTER 7

# CONGENITAL CARDIOVASCULAR MALFORMATIONS

## INTRODUCTION TO MALFORMATIONS GENERALLY

Before entering into the topic of cardiovascular malformations a preliminary word should be said about malformations in general. Much has been written and many questions have been asked about how such manifestations should be defined and classified, about their nature and causation, their history and meaning (of the many sources the reader may turn to for guidance in this complex field, two are unabashedly recommended, Warkany (1971) and Kalter (2003). For the purposes of this section it should merely be noted that everything that goes awry structurally during prenatal life is not of equal moment for the life and death of the organism. The broad division of congenital malformations into two categories clarifies this statement.

The first, called major malformations, are the abnormalities that are of such drastic departure from the norm that they cause or are associated with prenatal or perinatal death, require surgical or medical care soon after birth, or are gravely physically handicapping. The second are those called minor anomalies, and these are trivial or relatively trivial physical divergences from the typical, come in many forms, and are usually of little or no medical or cosmetic consequence.

## INTRODUCTION TO CARDIOVASCULAR MALFORMATIONS

Congenital malformations of the heart and great vessels, it is often said, occur more often than do malformations of any other organ system, with a frequency, according to some estimates, no doubt of great exaggeration, of as many as one in every 100 births. Many of them however, perhaps as many as half, consist of minor forms with little or no health relevance. It is well to recall these words: "The commonly accepted figure for the total incidence of congenital heart disease is approximtely 8/1,000 births. The majority of these conditions, however, do not pose life threats to infants; they may undergo spontaneous involution . . . may remain mild for several decades . . ." etc. (Nadas et al. 1973).

It will be the aim of the following pages to look into matters of the frequency of these malformations, its forms and degrees, in livebirths, stillbirths, fetuses, and its

mortality ramifications. It can hardly be doubted that proneness to maldevelopment of so embryologically complex a component of the body existed in primates from the moment the order emerged from the shadows of evolutionary time, and in fact in all mammals coincident with the evolution of the heart (Taussig 1982). But because cardiovascular malformations are not externally visible, in distinction e.g. to certain ones of the central nervous system, whose records go back millennia (Saint-Hilaire 1832–7, Warkany 1971, p 6 et seq.), it was only recently, as history measures time, that congenital defects of the heart and its adjuncts were first recorded and began to be studied (Lamy et al. 1957, Taussig 1965). (Ectopia cordis, it may be argued, is an exception, but it is not per se a cardiovascular malformation.) This covertness is only one of the qualities that make for difficulty in the pursuit of knowledge of their prevalence, nature, and origins.

## THE FREQUENCY OF CARDIOVASCULAR MALFORMATIONS

First of all, in the nature of things, one asks how often do things happen. For cardiovascular malformations the answer is complicated. If it is assumed that most if not all heart defects (as they will sometimes alternately be termed here) are already present at birth–and evidence indicates that there is no reason to doubt it–the primary question may reasonably be, what is their frequency at that time. But cardiovascular malformations, as already mentioned, are not externally visible and many do not present signs in early infancy or even later, so their presence must be recognized by special means. (This sets them apart from the other major segment of congenital malformations to be discussed in the further volume of this work, those of neural tube closure, which can usually seen by the naked eye and are easily recognizable at or about the time of birth.) Some may be inferred in the neonate, but most cardiovascular malformations are detected or recognized only some time after birth, which means that infants and even older children may need to be monitored for a time to determine their complete frequency. How long this should be and what may be the rate of diminishing return must be part of the consideration.

Complete determination is also hindered by various matters along the chain of life. Defects in abortions may not be noticed or appreciated, detection in embryos and fetuses by ultrasound and like techniques is often inefficient, while those in later fetal deaths may be overlooked or fail to be considered separately, making for distortions of frequency and type. In later infancy and early childhood some defects may remain undiagnosed or some vanish through spontaneous repair or death.

Faulty determination may also happen, in various ways. Hospitals that serve as referral centers may record an extraordinarily high congenital malformation frequency, even in neonatal deaths (e.g. Autio-Harmainen et al. 1983). In teaching hospitals, in contrast to general ones, autopsy material is usually selected (“. . . congenital malformations needing surgical repair are sent there from many hospitals”), and may yield deceptively high malformation frequency (Ahvenainen 1960). A different sort of error proceeds from negligent ascertainment. This is evident in the unrealistically low Swedish malformation rate of 0.6%, two-thirds

in perinatal mortalities, including anencephalus, cardiovascular abnormalities, etc., reported by Lindgren et al. (1962). Another type comes from a national survey comparing 1972 and 1975–6, with an increase of malformations in mortalities in that brief time from 18.4 to 26.4%, entirely owing to the increase in clubfoot, which must have been some unidentified individual's favorite diagnosis (Rumeau-Rouquette et al. 1978).

The purpose here, using studies chosen mostly to represent successive eras, will be to trace the advance in knowledge of the frequency of congenital heart malformations, achieved in part through the development of ever more sensitive external and invasive diagnostic methodology and by ever more experienced practitioners.

The earliest efforts, those to be regarded as community or population studies, were concerned with children of elementary and high school age, which in time were extended to preschool ages, while others were directed at hospital populations and infancy in all stages.

CHAPTER 8

# POPULATION-BASED STUDIES

## EARLY US STUDIES

The earliest attempts to find out how often cardiovascular malformations occur were made in school-age children in several localities early in the last century using the necessarily nonspecific means at hand. For example, in Philadelphia in the 1920s, grade- and high-school children were first examined by school medical inspectors, and those with definite or suspicious signs of heart disease were looked at more carefully at a cardiac clinic, using in addition to the stethoscope, the standard tools of the time, fluoroscope, electrocardiograph, cardiac response to effort, etc. (Cahan 1929). The estimate of "organic heart disease" arrived at was 6.9/1000 in the younger and 11.1/1000 in older children. But this was realized to be a great overestimate, due to including acquired as well as congenital heart disease. In fact only a very small fraction was found to be congenital, 0.9/1000; which on the contrary was an unrealistically low estimate, largely the result, as would later be revealed, of omitting those with severe defects who had died.

In Cincinnati in 1936-8 school physicians referred school-age children, 5-19 years old, suspected of having a cardiac abnormality to pediatricians "especially interested in cardiology" for examination by percusssion and auscultation of the heart and in doubtful cases with the then available instrumentation, electrocardiogram, teleoroentgenogram, and fluoroscope (Rauh 1939). The findings plus historical records gave an estimate of 1.5/1000 with definite evidence of congenital heart disease. Defects were noted at birth in 29% of cases and in another 25% between the 1st month and 2nd year. As would continue to be true over the years, in those in whom a diagnosis was possible the commonest types were ventricular septal defect and patent ductus arteriosus, which accounted for about two-thirds of the entire sample (See Rauh 1939 for citations to similar studies as far back as 1915).

A greater frequency, 2.8/1000, was found in parts of Colorado in 1949-51 in sixth-grade children examined by experienced pediatric cardiologists, the diagnosis not well described however nor the types of defects named (Dodge et al. 1958). Very early epidemiological differentiations noted a greater frequency in Spanish than Anglo children, in rural than urban residents, and in crowded than less

crowded living conditions, but the differences were relatively small and "probably not meaningful." Later such probings, to be gone into below, were seldom more productive.

Another study in Colorado is of interest because it was made in a western county of that state, half of whose population lived at an elevation of 4575 ft above sea level (Morton et al. 1959). Children mostly 6-11 years old were examined physically by experienced pediatricians and by electrocardiography, and those with suspected heart disease reexamined. The frequency was 5.3/1000 examined, the commonest defects being atrial and ventricular septal defects, pulmonary and aortic stenosis, ductus arteriosus, and coarctation of the aorta. Age at discovery was not mentioned, nor was the possible significance of atmospheric elevation to the pronounced increase in the frequency of some of the defects considered.

Heart-sound tape recording, a supposedly convenient means of mass testing for heart problems, was used on a random sample of high school children in metropolitan Chicago in 1962-3 (Smith et al. 1963). The findings were evaluated by trained physicians, and children were further examined when necessary; a frequency of 1.4/1000 taped children was found, doubled to 2.8/1000 total Chicago area high school population by extrapolation. The test thus proved of little usefulness.

A modification of the procedure was used in school age children in Michigan City, Indiana in 1962 with minimal success (Miller et al. 1965). Preliminary evaluation by auscultation, followed by tape recording of heart sounds, yielded a frequency of 2.4/1000; despite which the method was considered superior for evaluating mass populations, and even to surpass chest x-ray and electrocardiogram in detecting heart disease.

A final use in Colorado of the same procedure (one would have to look into the matter more closely to learn why this part of the nation was wedded to this methodology), combined with examination by pediatric cardiologists and electrocardiogram of children with suspected heart disease, yielded a frequency of 1.4/1000, hardly an improvement (Morton and Huhn 1966). The most frequent defects, called "relatively simple," ventricular septal defect, pulmonic and aortic stenosis, composed over 70% of the total. No socioeconomic or ethnic (white, Latino) differences were found.

A long-term registry in San Francisco begun in 1946 recorded the findings of periodic medical examination for cardiac handicap or a presumed one in grade-school children and others with a congenital heart defect, many confirmed by catheterization or operation (Mustacchi et al. 1963). By 1960 a frequency of 2.0/1000 children was estimated, with ventricular and atrial septal defects, patent ductus arteriosus, coarctation of the aorta, etc. the leading defects. Similar studies during the preceding 20 years (cited by these authors) indicated that the level of occurrence and of survival had been stable during this period. But this frequency was realized to be incomplete, and that other sources were needed to make a fuller estimate. Called upon in particular were death certificates of children born in 1949-51 with diagnoses of congenital cardiovascular malformations, which yielded a frequency of 5.9/1000 live births. The survival data observed for this cohort indicated that 7% died on the 1st day, 45% by 1 year, and only half lived beyond their 3rd birthday.

Two reports then appeared, almost simultaneously, each in apparent ignorance of the other, of estimates of cardiovascular malformations in infants and young children, both using the mortality records of the California Crippled Children Services. One, from the state department of public health, using the records of children dying in 1957-64 from congenital heart disease from birth to 8 years of age, calculated the supposedly conservative estimate of 4.5/1000 live births, approximating what more direct methods had generally discovered up to that time (Belloc 1968). The other, from the Kaiser Foundation Hospital Department of Pediatrics, a combined autopsy and population study of deaths in 1957-61 (Allen 1968), is discussed below.

Public health records are notorious for underrecording malformations. This was borne out by the low heart defect estimate, 0.6/1000 births in Philadelphia, found on death certificates, in the majority of instances of children born dead or dying in hospital (Murphy 1947), and of 0.4/1000 in live birth notices in British Columbia (Renwick et al. 1964); auxiliary infant death records raised the latter to 4.2/1000.

A birth certificate study of over 8 million white, single live births in the US in 1961-6 similarly yielded a low heart defect frequency, 0.6/1000, an obvious undercount, admitted to be so by the authors, its inadequacy clearly underscored by the poor Down syndrome record (Hay and Barbano 1972).

Information obtained from Oregon vital records for 1957-61 was also incomplete (Osterud et al. 1965). Entries on birth certificates indicated a heart defect frequency of 0.8/1000 live births, similar to that recorded on birth certificates in New York in that period (Hoffman 1968). The birth certificate inadequacy is emphasized by findings on death certificates from several regions, which gave a defect frequency of 2-3/1000 live births, the great majority under 1 year of age (Hoffman 1968).

These documents revealed that in mid-century infant mortality was a looming presence: cardiovascular defects comprised 52% of all deaths from congenital malformations, more than all others combined. Most deaths were associated with ventricular and atrial septal defects and patent ductus arteriosus. The order of malformation frequency identified on birth certificates was the reverse of that on death certificates, which for cardiovascular defects is a rough indication of the relatively small proportion recognized at birth.

Data derived from vital statistics regarding neonates in New York City in 1958-9 indicated a frequency of cardiovascular malformations of 1.8/1000. This relatively low figure is obviously explained by the source of the information, and give support for its mistrust (Erhardt and Nelson 1964).

The usefulness, or otherwise, of death certificates, referred to here and there throughout this work, may be mentioned parenthetically. A study that was concerned with this question, if only indirectly, compared reports of children with cardiovascular defects noted on New York State death certificates with diagnoses recorded in an Albany Medical Center pediatric cardiology registry during a six and a half year period (Hook et al. 1977). Analyzing the respective records, the authors concluded that while death certificate reports can monitor trends they fail to provide information about death from specific defects.

A combined autopsy and population study of deaths in California in 1957-60, as in New York, found an untrustworthily low heart defect frequency, of 1.8/1000 live births in infants under 1 year of age, but similar to the 1.7/1000 found in a previous period in California (Allen 1968). About 50% of the deaths occurred in the first 2 days of life and two-thirds under 1 year. The most frequent anomalies as usual were ventricular septal defects and patent ductus arteriosus; but in the earliest deaths the most common was coarctation of the aorta. Death from cardiac anomaly was different from all infant deaths however, in mostly occurring after the 1st week of life; and occurring in a lower proportion of premature births, 6%, than occurred in all births in California in the period surveyed. Almost 20% of the affected infants also had noncardiac malformations, about one-fifth of them Down syndrome. The frequency of heart defect types in the latter was enumerated, but did not include atrioventricular septal defect; although elsewhere in the paper this defect was noted as having occurred in 0.33/1000 live births, an improbably low figure. Epidemiological analyses made of the etiological correlates of the defects will be discussed below.

## TORONTO STUDIES

Before discussing later population studies, an impressive series conducted in Toronto beginning soon after the second world war is considered in detail (Gardiner and Keith 1951). A registry set up in the city public health department collected information from all available sources about pre- and public-school children with a possible cardiac abnormality or history of rheumatic fever. They were examined at the Hospital for Sick Children, with "new surgical technics," electrocardiography and fluoroscopy, and when indicated also with angiocardiography and heart catheterization. The estimated frequency in 1948-9 of congenital cardiovascular malformations in children 5-15 years old was 2.1/1000 and in those from birth to 5 years, 2.3/1000, the modest increase over the findings of other studies attributed to greater interest and "a more intense search." Only 15% of cases were discovered in the 1st year of age, 36% of which died in the 1st month and another 20% in the remainder of the year. The most frequent diagnoses were ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot. According to cause of death tetralogy was first, transposition second, etc. Thus the first set, the authors commented, should be of interest primarily to pediatricians and the second to surgeons.

A later report from Toronto of children up to 15 years of age referred to the registry in 1961-2, examined clinically and by electrocardiograph and radiograph if required, found cardiovascular malformations in 3.0/1000 births in all ages, 2.6/1000 in ages 5-15 and 3.7/1000 in 0-5 years, the latter somewhat larger one attributed to possible "increased diagnostic acumen of cardiologists" (Rose et al. 1964). A mere 8.5% was discovered in the 1st year of life; two-thirds dying under 1 month of age. The commonest defects were ventricular and atrial septal defect, with pulmonary and aortic stenosis and tetralogy of Fallot next in order of frequency. Thus in the

13 years between the first and second surveys only a modest overall increase in the frequency of congenital heart disease was discovered.

The next report however told of considerable progress (Keith 1978). Based on material available at the Toronto Hospital for Sick Children regarding lesions coming to the attention of pediatric cardiologists and cardiac surgeons in 1950-73, the overall frequency in children up to "many years" of age was 6.7/1000 live births, significantly greater than previous findings. A remarkable fact here is that although this estimate was based on data accumulated over a period of 24 years, and therefore apparently included the findings of the two earlier reports noted above, the greatly increased frequency, more than twice that reported in 1964, must be attributed, by far, to cases ascertained solely in the most recent decade surveyed.

A calculation finds that 94% of the cases were collected in this period, the very large proportion due it may be to the hospital's active referral practice, where "diagnostic laboratory and surgical expertise has been established [which] encourages physicians to refer patients" especially with certain types of defects. And it is the relatively large number of these sorts of abnormalities, besides the ordinarily common ones, that perhaps led to the relatively great frequency of defects found. One of these, bicuspid aortic valve for example, had a frequency of 12.8/1000, seven times more frequent than ventricular septal defect, and inordinately more frequent than was found in a conventional population study, where its frequency was 0.7/1000 (Ferencz et al. 1997). The high overall frequency may thus have been due largely to including this defect, which occurred in 1.3% of all live births, and is usually omitted in studies of heart defect frequency (Hoffman 1995). Also more frequent than usual was tetralogy of Fallot, whose elevated presence was attributed to being discovered by a referral center, a potential source of exaggerated reporting.

Early mortality of children with cardiovascular malformations was high in Toronto. In 1950-70 just over one-third died in the 1st month and a like percentage in the remainder of the 1st year. The predominant types of defects in the earliest of these were mitral and aortic atresia and stenosis, coarctation of the aorta, and transposition of the great arteries. The large number of different hereditary disorders and syndromes in which congenital cardiovascular malformations may occur was listed, as part of a discussion of the familial frequency of heart disease; but associated defects in the cases and their effect on the malformation frequency were not mentioned. The subject of associated malformations will be discussed below.

## BRITISH STUDIES

Introducing the subject here is an account of a historical overview from 1912-67, taken from the Annual Reviews of the Registrar General of England and Wales, during which period there was noted an overall frequency of congenital cardiovascular malformations in infant death of 1.7/1000 live births (Rogers and Morris 1969). Large and significant secular variations were registered which supported the possibility that environmental factors were important in the etiology of these

conditions, but offered no insight into what they might be, a subject to be delved into below.

Population studies of congenital heart malformations in children were made in several British localities over the course of many years. One of the longer ongoing ones was initiated by a study of children born in Birmingham in 1940-9 (MacMahon et al. 1953). This like many other similar studies began with the prospective gathering of information from various sources, such as hospital and school physicians, but also from postmortem records and death registers, following its subjects from birth to age 9, the great majority however, two-thirds, died before 1 year of age. The mean frequency of cardiovascular malformations, 3.2/1000 total births, fluctuated appreciably from year to year, even within the earliest 6 years of the survey, those with the most complete ascertainment, when on average it was greater than in the later years, 3.6 vs 2.7/1000 total births. The errors of observation that may have affected this estimate were evaluated and found perhaps to have led only to a slight overestimate. [A commentor felt otherwise (Hay 1966).]

Differing from many other studies, heart defect findings were reported in still-births, but whose frequency, 1/1000, was a great underestimate. This was no doubt due at least in part to the low postmortem rate; which was made evident by comparison with frequencies usually found in stillbirths, as described elsewhere in this work. This may explain Carlgren's (1959) puzzlement that "it is hard to understand why the incidence should be lower in stillborn than liveborn infants." A difference still puzzling years later.

Other findings were less in dispute. Similar to other studies, the most frequent abnormalities in autopsied cases, probably the ones most accurately diagnosed, were septal defects, patent ductus arteriosus, and transposition of great vessels, which accounted for 44% of all defects. Nevertheless the fact that a relatively low frequency was discovered even in children followed from birth to age 9 seemed to indicate that lengthy follow-up was insufficient for complete ascertainment.

The continuation of the Birmingham story is helpful in several regards. An interim summary noted that the frequency of heart malformations in those seen soon after birth, 2.1/1000, became 4.2/1000 after a 5-year follow-up (McKeown and Record 1960). A later report supplied additional details (Leck et al. 1968). Supposedly complete ascertainment of all congenital malformations, relying on numerous sources of information, was accomplished by following children born in 1950-4 to 6 years of age. The frequency of cardiovascular malformations was 4.2/1000 total births, which supported the earlier finding that the frequency in the 2 weeks following birth was about half that amount, and appeared to confirm that lengthy follow-up was needed for more complete ascertainment. Even so, this was almost certainly still an underestimate, regardless of having been compiled from multiple though overlapping sources, mostly obstetric summaries.

Interesting data supplied about malformations in mortalities must be noted. Of children born alive in 1950-9 1.6% died early neonatally, of whom 23.1% were malformed, which was 19.4% of all malformed. The same for stillbirths were 2.2, 20.6, and 23.7%. As to ascertainment of malformations, 58% were discovered

through stillbirth notification, death certificate, and necropsy report. Similar information about cardiovascular malformations was not given.

## ASSOCIATED NONCARDIAC MALFORMATIONS

This is an opportune point to take a 'time out' to discuss the subject of the association of noncardiac malformations with cardiac ones. Two questions are raised by this matter, the practical one of whether heart defects that are associated with noncardiac defects should be included in estimating the frequency of heart defects, and the theoretical one of the nature of such associations. In the MacMahon et al. (1953) study detailed above, associations occurred in 21% of the approximately three-quarters of the cases with complete records, comprising a wide variety of abnormalities, the most frequent being Down syndrome, whose most common cardiac defect was "septal defect."

The present writer believes that malformation clusters, especially when they include noncardiac defects with a known etiology, such as Down syndrome (Lejeune et al. 1959), should not be included. The argument was put as follows by Czeizel et al. (1972): "It is highly probable that the isolated and multiple types of congenital defects belong to fundamentally different categories. Isolated cases usually represent separate nosological types, whereas multiple cases often represent combinations of syndromes with different aetiologies." Regardless of whether multiple cardiac defects or cardiac defects associated with noncardiac ones were being referred to, the principal is the same. That is, that multiple defects, varying in composition and frequency according to circumstance, are etiologically apart from isolated ones, and therefore for the purpose of comparison from study to study and of measuring progress in time, isolated or intrinsic cardiovascular malformations must be the unit of comparison. A further purpose, to be dealt with below, is to clearly define the subject to examine its etiology and epidemiology.

But there is also the fundamental question of the nature of such associations. It is widely reported, as Warkany copiously documented (1971, p 568 et seq.), and as will be seen below, that cardiac and many different noncardiac malformations often occur together. But why this is so it appears has seldom been considered. One of the rare attempted explanations held that "[A] malformation of one part of the body may lead to maldevelopment of another part of the body" (Leck et al. 1968), without pondering how this may happen; except, as the quotation continues, "as in the example of the foot deformity that results from the impairment of function of the spinal cord owing to myelocele." The latter is a sequential example, but others may be coincident.

It was once a subject much debated, how single etiological factors may produce combinations of malformations. Multiple effects, or pleiotropism, was intensively investigated by the geneticist Hans Grüneberg (1938, 1963), employing the manifold morphological effects of mutant genes in the rodents that were the subjects of his interest. He concluded that the genes (and this applies to etiological factors of any variety) simultaneously cause multiple abnormalities either, to use his terminology, by coordinated action on different parts of the body or by subordinated ones, i.e.

"a cascade of secondary and tertiary gene effects with a hierarchy of causes..." It is probable that all human and animal teratogens, whether genic, chromosomal, or environmental, are confined to the same courses of action. Which of these pathways, if this is so, leads to the multiple effects associated with heart malformations?

It has been asserted that "the incidence of other [i.e. noncardiac] defects...is of course much higher...than in the general population of births" (MacMahon et al. 1953), that "the associations were more common than would be expected by chance" (McKeown and Record 1960), that "[E]xtracardiac malformations occur more often in children with congenital heart disease than in the general population" (Warkany 1971, p 568). However, one may be permitted to doubt whether the general population is appropriate for the comparison.

If this increased frequency indicates that the conjunction of cardiac and other malformations does not happen randomly, it follows that proneness to cardiovascular malformation makes for vulnerability to additional maldevelopment. Two questions, direct and indirect, follow: what is the basis of the so-called vulnerability; and is the vulnerability unique to cardiovascular malformations. The latter may be tested by comparing the association of cardiovascular malformations and not cardiovascular malformations with that e.g. of central nervous system malformations and not central nervous system malformations.

A detailed analysis of the findings of a Birmingham survey is of great help in pursuing the question, since it listed all associated malformations occurring more than once that were discovered during the entire follow-up period (Leck et al. (1968). This showed that 31.2% of individuals with cardiovascular malformations had associated abnormalities, 34% of them Down syndrome, 18% lower limb (mostly clubfoot), 12% gastrointestinal, 10% oral cleft, 6% neural tube defects (anencephaly, spina bifida, encephalocele), etc. Making the same analysis for neural tube defects 29.6% were associated with other defects, 45% clubfoot, 5% cardiac, 2% Down syndrome, and the rest a miscellany of conditions. A statistical test of the two proportions (125 occurrences of associated defects in 400 cases of cardiovascular malformations [125/400] vs 128 occurrences of associated defects in 433 cases of neural tube defects [128/433] found $\chi^2 = 0.28$, $P \leq 1.0$. Thus the frequency of malformations associated with one defect type was not statistically significantly different than with the other, indicating that both were equally prone to the occurrence of associated defects; and hence that cardiovascular malformations are not unique in this respect, while however the assortment and proportion of associated defects was largely different for each.

Nevertheless, it is interesting to attempt to explain some of the associations. For example, the limb damage (almost all clubfoot) accompanying spina bifida is readily understood as sequential, due to the nerve damage associated with that malformation; as Neel (1958, p 431) expressed it, "[C]lubfoot has been excluded as an "associated defect" because of the fact that in most instances it is only another manifestation of the nervous system malformation." The preponderant association of cardiovascular malformation with Down syndrome is also easily explained, but as coincident not sequential events, cardiovascular malformations being a frequent

component of that chromosomally caused syndrome. In this case, as in that of the neural tube defects, the cardiovascular malformations in Down syndrome are not independent occurrences, and thus are not to be counted in the total. Isolated cardiovascular malformations, i.e. those unaccompanied by noncardiac defects, therefore should be the central focus of an examination of the frequency of congenital cardiovascular malformations.

Reports of the association of cardiac and noncardiac malformations, and of their possible meaning, have continued over the years, up to the present, e.g. Emerit et al. (1967), Noonan (1978), Kramer et al. (1987). Many of them were cited by Pradat (1997). This author also contributed to the quest of identifying specific relationships by analyzing all infants identified by malformation registries born in Sweden in 1981-90 with major cardiac and at least one noncardiac defect diagnosed in the 1st year of life. Excluding those of chromosomal origin or comprising a recognized malformation syndrome, about 15% of the infants with cardiovascular malformations were also found to have noncardiac defects, about as many as has often been found by others; but aside from a possible combination of spleen anomalies and atrioventricular septal defects, also previously reported, no indisputable one was discovered. As the author recognized, "the large number of tested hypotheses make it difficult to exclude chance associations."

It is apropos to conclude this matter by noting that not only the basis of the association of cardiac and noncardiac malformations was long debated, but that of the concurrence of malformations generally was a much pondered question; with a panoply of suggested explanations, described in detail by Evans and Polani (1980), none of which satisfactorily settled the puzzle.

## FURTHER BRITISH STUDIES

A brief comment may be made about the two consecutive studies, described above, conducted in the same geographical area (MacMahon et al. 1953, Leck et al. 1968). Both included children of a considerable span of age, but had somewhat different results; the earlier found a frequency of congenital cardiovascular malformations of 3.2/1000 births in children from birth to 9 years, and the later 4.2/1000 births in children to 6 years (in the latter the cardiovascular malformations were not specified). The difference could hardly have been due to the length of the follow-up, since most defects are discovered in the 1st year. Neverthless, even the larger is smaller than intense methodology sometimes later revealed.

The findings of a broad national survey (Butler and Alberman 1969) largely supported the Birmingham findings, and are briefly recounted. In children born in Britain in the Spring of 1958, cardiovascular malformations were diagnosed in the 1st week of life in 2.8/1000 births, being 16% of all malformations. Of the cardiovascular malformations, over 70% occurred in stillbirths and neonatal deaths, and only about one-third were single malformations. Including later deaths, the total frequency of cardiovascular malformations was 3.9/1000 to 7 years of age. Making certain assumptions and extrapolations the frequency of those with definite heart

disease at different ages was estimated to be 6.4/1000 at 28 weeks of pregnancy, 5.9/1000 in livebirths, 4.5/1000 at day 28, with diminishing frequency to 3.4/1000 in schoolchildren, the last following deaths in the intervening years. The last may have been low, the true frequency being 4-5/1000.

To continue. A Congenital Abnormalities Registry was begun in Liverpool in 1959 to receive notifications by pediatric registrars and obstetricians of the births of malformed babies (Smithells 1962). The information was used as the basis of an attempt to establish the frequency of cardiovascular defects (Hay 1966). Live births in 1960-4 reasonably certain to have cardiac malformations had a frequency of 4.7/1000. The commonest defects, ventricular and atrial septal defect and patent ductus arteriosus, accounted for more than half the total; the first of these, the most frequent of all, at 34%, had the smallest mortality rate during the follow-up period, while the commonest among the deaths, transposition of the great vessels, pulmonary atresia, and common truncus arteriosus, were among the least common at birth. A supplementary report, of a "true population" survey, of defects in children followed to age 5-6 years noted a barely greater frequency, 5.0/1000, the types and means of diagnosis undescribed (Smithells 1968).

A further investigation in Liverpool of cardiovascular malformations, based on information gathered by the Registry, was made in children born in 1960-9 followed up for 3-12 years (Kenna et al. 1975). Those with suspected or definite congenital heart disease were referred to the children's hospital pediatric cardiology service, with diagnosis confirmed by clinical and investigative procedures and autopsy. A presumably complete estimate gave an average of 6.6/1000 total births, similar to many other contemporary findings. Omitting the first and last years of the survey, those of presumably incomplete ascertainment, gave a frequency of 6.9/1000, during which it still varied from 5.8 to 7.8/1000. The appreciably greater rate than that previously reported from the area (Smithells 1968) was assumed to have been due to the prolonged and intense study. Once again, the most frequent anomalies were ventricular and atrial septal defect and patent ductus arteriosus, with pulmonary stenosis and coarctation far behind, close to findings in other population studies.

The frequency of heart defects in stillbirths was relatively small, only twice that in a randomly chosen control group of nonmalformed children, 3.2 vs 1.5% in cases, and for this reason the frequency in all births was hardly different from that in live births, 6.6 vs 6.4/1000. That of defects in neonatal death, however, was significantly greater, 17.9 vs 1.0%, the most common being transposition of the great vessels, ventricular septal defect, coarctation of the aorta, and truncus arteriosus, totaling over 40%. As for birthweight, twice as many with defects weighed 2500 g or less (20%), i.e. were immature, as this is measured, as did controls (9%). This is among the few times in this work that the topic of some importance, birthweight and congenital malformation, was mentioned. It will require following up.

Continuing with this report, associated malformations were recorded in about one-fifth of all cases, which it was asserted was almost 10 times "the chance expectation." But because they were listed by individual defect rather than by affected individual, only for the most specific of them, Down syndrome, can the

relative frequency in cases and controls be examined. This was found to occur more than 30 times as frequently in the former than the latter. This is not a legitimate comparison however, first because cases were reported not because they had the syndrome, but because they had a heart defect, but especially because the comparison was made not with the controls but with the entire population. Omitting the cases of Down syndrome reduced the overall frequency of cardiovascular malformations to 6.2/1000 births. The greater part of this report was concerned with epidemiological matters, which will be discussed below in the section devoted to that subject.

A later consideration of cardiac malformations in children born in Liverpool in the same 1960-9 period, diagnosed clinically and by autopsy or catheterization, a study made to estimate surgical needs, yielded an updated frequency of 7.0/1000 live births (Dickinson et al. 1981). However upon excluding patients lacking definite evidence of congenital heart disease the frequency was lowered to 5.5/1000 live births, over half diagnosed neonatally and almost one-third at autopsy. Two defects, ventricular septal defect and patent ductus arteriosus (a suspect defect here and elsewhere for reasons broached discussed below), alone added up to 44% of the total. The study focused on estimating the number of needed operations for congenital heart disease, and for that pragmatic purpose, apparently, small spontaneously closing ventricular septal defects were discounted.

In an article whose purpose was to describe the Liverpool registry a table was included that noted the frequency at birth of congenital cardiovascular malformations in each of the years 1979-84, without further details, which appeared to indicate a decreasing trend (Owens et al. 1988). This was explained in part by a later report in which, widening its purview, the registry received prospective reports from various sources in the county of Merseyside, which included Liverpool and four surrounding districts (Jackson et al. 1996). Liveborn children with suspected or proven cardiovascular malformations, the majority up to 3 years of age, identified in 1979-88 were referred to the Cardiac Unit of the Children's Hospital and the diagnoses validated by the gamut of procedures, echocardiography, cardiac catheterization, intraoperative inspection, or autopsy. The overall frequency of congenital cardiovascular malformations, 7.6/1000 live births, varied annually from a low of just over 6/1000 in 1979 to a high the very next year of about 9/1000.

The most frequent abnormality, ventricular septal defect, occurred on average in 36% of all cases, which was greater than often reported, and 30% after excluding those in whom it closed spontaneously, mostly in the 1st year; but strangely it was greater, over 40%, in 1979, when the total frequency of cardiovascular malformations was lowest, and far lower next year when it was very high, the attempted explanation of which was based on cross-sectional echocardiographic nonavailability. The next most common defects, pulmonary stenosis and patent ductus arteriosus, together with the first amounted to 54% of the total. Almost one-fifth of cases died before 3 years of age, the majority in the 1st year, but no account was given of the defects associated with death or survival.

It may be remarked that the categorizing in this article of cardiovascular malformations by presumed morphogenetic mechanism, and the defining of groups of defects by this theoretical scheme, as was tabularly attempted in this paper, while giving the article the veneer of being up-to-date, was of no purpose in furthering morphogenetic or epidemiologic understanding of these malformations. Procrustean application of this theory to explain intra-area variation in heart defect frequency, as a possible means of clarifying the sometimes wide variation reported in previous studies, predictably, was of as little use as it has as yet proved to be in explicating pathogenesis.

Moving to another region, a survey in South Wales registered congenital malformations collected from numerous and sometimes overlapping sources, such as hospital records and birth, stillbirth, and infant death notification forms, in children up to 2 years of age born in 1964-6 (Richards and Lowe 1971). Though the findings were not separated by perinatal segment, the latter could largely be inferred. The frequency of cardiovascular malformations was appreciable, 4.4/1000 births (16% of which was ascertained from stillbirth or death registration). The predominant specified anomalies were septal defect and patent ductus arteriosus, but the findings in children of different ages were not stated separately, so again it is unclear whether the last one was an acceptable entry.

Added later was the information that the heart defect frequency included those in the many cases of Down syndrome (Richards 1973). The focus of the later study was the time of death of malformed individuals, from late fetal through the 1st year of life. In this population the usual order was reversed, neural tube defects being more frequent than cardiovascular ones, without doubt because of the relatively high frequency of the former in this region (Laurence et al. 1968). As for the perinatal mortality rate of the two malformation types, two-thirds of infant mortalities with neural tube defects died perinatally, while slightly more than half of all those with specified cardiovascular malformations survived the 1st year, ranging from no survivors with coarctation of the great vessels to 59% for septal defects.

In a survey of births in 1957-71 in the urban and rural district of Blackpool in North-West England congenital cardiovascular malformations were diagnosed with the then standard fourfold procedure of clinical examination, cardiac catheterization, surgery, and autopsy, the last accounting for half of the defects (Bound and Logan 1977). The frequency from birth through about 3 years was 5.8/1000 live births; with stillbirths included it was 6.8/1000. The frequency, fairly constant over this period, was similar to that in large English cities. Excluding Down syndrome the frequency was 6.6/1000 total births. Seventy-four percent of the cases were recognized by 3 months of age, 82% by 1 year, and 90% by 3 years. The most frequent anomaly by far in all as well as in live births, was uncomplicated ventricular septal defect, at 28% of all defects or 1.9/1000 births; whose frequency steadily increased throughout the period surveyed, doubling from 1.1 to 2.2/1000, which was claimed to be a "real increase..." which is no explanation at all. The frequency

of some anomalies apparently declined while others increased, e.g. atrioventricular septal defect associated with Down syndrome.

Information received by the Glasgow Register of Congenital Anomalies from multiple sources in 1973-86 was analyzed for various purposes (Stone 1989). The frequency of cardiovascular malformations in all births and terminations diagnosed at various ages was 6.5/1000, with no difference between 1973-9 and 1980-6. No further data were reported. One of the particular aims of the Register was to detect epidemics of congenital malformations caused by new environmental teratogens, in which it failed, as have all other such programs, not because of its imputed limitations, but because of, as it itself recognized, "an absence of epidemics" (Stone and Hamilton 1987).

## SCANDINAVIAN STUDIES

Reports from different parts of the world are helpful for comparative purposes. A program carried out in Sweden over the course of many years is illustrative. The first report concerned children with certain or suspected heart disease born in Gothenberg in 1941-50 (Carlgren 1959). It was based on reports to the cardiology clinic of the local children's hospital from school officials, child health center physicians, and general practitioners of children from birth to 7 or more years of age. The diagnosis in most survivors was made clinically or by electrocardiogram, while in most deaths it was made by autopsy and heart catheterization. About one-third were diagnosed neonatally and about half before 1 year of age. In these cases the frequency of cardiovascular malformations was 4.4/1000 births. In these plus those followed up to 7 years the frequency was 6.4/1000 live births, the large figure attributed to a combination of uncertain diagnosis, the long follow up, and the inclusion of apparently minor defects. Omitting those with associated malformations including Down syndrome reduces the overall frequency to 5.3/1000, and that in 1st-year survivors to 1.8/1000. The frequency in stillbirths, 0.7%, was an underestimate, due as was acknowledged to sparsity of autopsy records.

The commonest defects in the survivors were patent ductus arteriosus, pulmonary stenosis, and ventricular septal defect, and in cases dying in the 1st year coarctation of the aorta, ventricular septal defect, and transposition of the great vessels. Many of the mild or clinically insignificant ventricular septal defects were omitted in the frequency estimation. All defects in survivors and mortalities were listed in appendices. It is of interest that over half the Down syndromes died (at unstated ages) and it was probably in the latter that some of the 2.7% of atrioventricular septal defect occurred. The subject of this defect in Down syndrome is fully discussed below.

In the following 10 years, 1951-60, employing the same diagnostic procedures, the frequency increased significantly to 7.7/1000 live births (Carlgren 1969). But excluding the 18% of small ventricular septal defects–ones that can be considered minor and harmless anomalies–that closed spontaneously in the earliest years of life, reduced the heart defect frequency to the original 6.4/1000. Excluding cases

with associated malformations, including Down syndrome, further reduced the frequency, but to an unclear extent.

Again the most frequent isolated defect was ventricular septal defect, at 35%, but some significant number of these closed spontaneously, as noted above. Next in frequency were atrial septal defect, transposition of the great arteries, and tetralogy of Fallot. The frequency of low birthweight was significantly greater in children with cardiovascular malformations other than small ventricular septal defects. Mortality of children with defects at 1 year of age also appeared to decrease, from 2.0/1000 live births in 1941-59, to 1.9 in 1951-60, to 1.6 in 1961-5; with the disclaimer however, that for "pure cardiac defects" (undefined) there were no differences in this entire period. About 80% of deaths occurred in the 1st year. It must be noted that a contradiction appeared in this report, namely that the frequency in both periods combined, 1941-60, was 6.1/1000.

These frequencies can be contrasted with that uncovered by a nationwide register of congenital malformations in infants in Sweden in 1964-6 (Källén and Winberg 1968). With various qualifications and exclusions, e.g., of Down syndrome, the frequency of single cardiovascular malformations found during the maternity hospital stay was 0.85/1000 and of such defects combined with associated ones, 1.25/1000, smaller than the 4.4/1000 estimated in infancy in Gothenberg. This may indicate that for these malformations at least, the methodology of the registry, as diligent as it appeared to be, was faulty; or that some cardiovascular malformations failed to present symptoms at the early age surveyed. In either instance, the intention that registration would serve as an early teratogen warning system was found unavailing.

The limitations of the congenital malformation registry were explained with the establishment in the 1970s of a computerized registry of all delivery records in Sweden (Carlgren et al. 1987). The principal finding, gathered from the four components of the registry, was that in 1981 the frequency of congenital cardiovascular malformations diagnosed before 1 year of age was 9.1/1000 total births. This obvious overestimate was made more realistic by excluding various doubtful conditions (especially patent ductus arteriosus in infants of less than 2500 g birthweight), as well Down syndrome and various other syndromes with a high incidence of cardiovascular malformations, which reduced the frequency to 6.7/1000 total births.

The components of the registry differed greatly, however, in estimating heart defect frequency, depending on malformation inclusion and age range surveyed. For example the Registry of Congenital Malformations found a low frequency, about 1-2/1000, not surprisingly since its reports were confined to early neonates and based on cyanosis and heart failure; while the Medical Birth Registry, which also collected 1st-week reports, relied on clinical diagnosis, and excluding the patent ductus arteriosus mentioned above found a frequency of 5.2/1000. The workings of some epidemiological features will be discussed below.

Data from the two Swedish sources mentioned, the Registry of Congenital Malformations and the Child Cardiology Registry, were used to analyze findings in children born in 1981-6 (Pradat 1992a). In sum, together they reported the frequency to be

2.8/1000 births diagnosed in the 1st year of life. Several incidental facts are of interest. The first source reported 12% of the cases and the second most of the remainder; but it is apparent that the former on the whole reported more severe cases, since almost two-thirds of them died perinatally, while this was true of only 8% of those reported by the latter. Twelve percent of the infants had a known chromosomal anomaly, of which the great majority, 83%, were Down syndrome, and over half of the latter had atrioventricular septal defects. This and a companion article (Pradat 1992b) were much concerned with epidemiological matters, which will be described below.

There followed reports from Sweden on various related topics, also described below, and most recently one that focused on obstetric outcome (having exhausted other facets of the problem of cardiovascular malformations), which also documented some findings of interest here (Cedergren and Källén 2006). As identified by the registries mentioned above the frequency of isolated and nonisolated congenital cardiovascular malformations up to the age of 1 year in singleton births in 1992-2001 was said to be 9.1/1000, although it was not clear how this figure was derived. While some few things were excluded from the analysis, lesser forms of defects must have been included, as indicated by the statement that "congenital malformations as a whole" were used to evaluate various associations. The indiscriminate assortment of defects accepted into the analysis, necessitated by the need to enlarge numbers in order to "demonstrate...weak associations" with obstetric and neonatal outcome, certainly made for a flawed overview of heart defect frequency, but in addition could even have weakened the primary focus of the study. Further indicating a blanket admixture is the very high level, over 13%, of the ordinarily rare atrioventricular septal defect.

This may be the appropriate place to note the high frequency of cardiac malformations discovered in Eskimo children in the self-governing Danish possession of Greenland (Harvald and Hels 1972). In children born in 1957-64 in the capital city, Godthåb, now Nuuk, as ascertained by clinical examination, hospital records, and health and death certificates, the frequency in those 1-10 years of age was 18.5/1000 live births, over 40% ventricular septal defect. Attempts to explain this finding centered on the significantly elevated age of the mothers of the cases and the low socioeconomic situation of the Eskimo population, but not too convincingly.

The frequency in Tonsberg, Norway of congenital heart defect in children born in 1982-96 was 10.0/1000 live births, three-quarters diagnosed before leaving hospital (Meberg et al. 1999). Almost half of the others, the 'missed' ones, diagnosed at a median age of 6 months, had ventricular septal defect. Judging from the low mortality rate in the late-detected ones, 1.2% vs 13.8% in the others, these and other defects in them must have been of a lesser degree, in the category of minor defects, as would also be indicated by the high frequency noted.

Various centers in Vestfold County of Norway collaborated to obtain epidemiological data about children with heart defects born in the area in 1982-96 (Meberg et al. 2000). All liveborn children were investigated before discharge from hospital and those suspected of having a heart defect were echocardiographed, etc., with

pulse oximetry added to the standard procedure in 1986. Those with a heart defect were followed periodically thereafter for 3-18 years. The overall heart defect frequency in offspring born during this period was 10.2/1000, 75% detected before discharge from hospital. The most common were ventricular septal defect, at 59% (most of which closed by 1 year, 82% muscular, closure occurring in 74% of them), atrial septal defect, 8%, and numerous others, including atrioventricular septal defect, at 3%. Associated defects, chromosomal, etc. occurred in 20% of the cases, the largest proportion Down syndrome, how many with the atrioventricular septal defect not indicated. It must be of some theoretical significance, for the future to illuminate, that significantly fewer associated defects occurred in cases with ventricular septal defects than others, and that significantly more of them were in conjunction with the membranous than muscular ventricular septal defect.

A significantly larger fraction of the ventricular defects closed in the later years of the survey than in the earlier ones, indicating that increased closeness of the scan discovered many minor degrees of the defect ("improved diagnostic methods and strategies for finding small [ventricular septal defects] in the muscular part of the septum"). Omitting those that closed by 1 year, i.e. those considered minor anomalies, reduced the total heart defect frequency to 6.0/1000.

## VARIOUS OTHER EUROPEAN STUDIES

Associations of cardiac and noncardiac malformations were analyzed in the North Rhine region of Germany in children up to 16 years of age in 1981-2 (Kramer et al. 1987). Of these children 53% had an associated noncardiac malformation, a much larger fraction, in fact the largest fraction, than ever reported, which may indicate that the children were selected for the severity of their condition. Thus it can hardly be considered representative of the matter at all.

In the neighboring districts of Erfurt and Suhl in the then East Germany cardiac examinations and autopsy protocols of all deceased children found an overall frequency of structural cardiovascular malformations of 7.1/1000 live births in children 5-15 years old born in 1971-80 (Schmidt 1989). The rate was fairly constant from year to year, but differed significantly between the districts, being on average 9.7/1000 in the former and 5.9/1000 in the latter. The most frequent abnormality apparently was ventricular septal defect, which comprised 35% of all the defects, but was more common in Erfurt than in Suhl. Few other defect types or other relevant details were mentioned.

Moving eastward, in Budapest in 1963-5, in a multisource study of still- and liveborn children up to the age of 7 years, as determined by autopsy, surgery, and "up-to-date cardiological examination (catheterization, etc.)," a frequency of congenital cardiovascular malformations was found of 7.1/1000 births (Czeizel et al. 1972). Over one-quarter of cases died neonatally and another fifth during the remainder of infancy. The frequency of defects in neonates was not stated, but a table revealed that 59% of affected children died, that the frequency of defects in

stillbirths and neonatal deaths combined was 1.9/1000, and in 1st-year mortalities (86% of all such deaths) 3.6/1000.

Associated malformations, which undoubtedly occurred, were not mentioned, except for instances of Down syndrome with cardiovascular malformations; omitting which lowered the overall frequency to 6.4/1000, in accordance with the author's own opinion, detailed above. As in other populations, over half of the defects consisted of ventricular and atrial septal defects and patent ductus arteriosus.

A small-scale study in a rural district of Hungary turned up an unusually high frequency of cardiovascular malformations in school age childen born alive in 1963-5 (Mészáros et al. 1975, 1980). Verified defects occurred in 10.6/1000 births or 7.6/1000 isolated cases, for which several unlikely explanations were offered. More likely, conditions that were not severe may have been included, perhaps indicated by the fact that "neither parents nor teachers had any knowledge of the condition..." Comparing individual defects in the regional population with the metropolis of Budapest (Ferencz et al. 1990a), showed that proportionately almost all the specific defects were not more frequent in the former than the latter; hence the difference was not due to any one defect, e.g. ventricular septal defect, being more often diagnosed; nor was it likely that diagnostic acumen differed. The mystery persisted.

A comprehensive study was made in the central European region of Bohemia of children born in 1980 (Samánek et al. 1989). They were examined at birth, periodically in infancy, and finally at 4 years of age, and those suspected of having a cardiac abnormality referred to a pediatric cardiologist. This repeated specialized examination found cardiovascular malformations in 6.4/1000 live births, 74% verified by 4 years of age at surgery or a pediatric cardiology center, and the remainder at autopsy. Twenty-six percent died by 4 years of age, but the defects in them were not designated. The four commonest defects, ventricular septal defect, atrial septal defect, aortic stenosis, and pulmonary stenosis, comprised 58% of the total, almost one-third ventricular septal defects alone. Among the rarest defects was atrioventricular septal defect, at 4.1% of all defects.

A preliminary report of congenital cardiovascular malformations in Emilia-Romagna, a northern area of Italy, briefly described the findings of a malformation registry (Magnani et al. 1994). The frequency of defects detected in the 1st week of life in births in 1982-92 was 4.1/1000. A fuller report appeared in time. Congenital cardiovascular malformations in all births in 1980-94 were ascertained prospectively by the said malformation registry (Calzolari et al. 2003). Cases were referred to a secondary center for specific diagnosis, which was confirmed mostly by echocardiography, surgery and/or autopsy. The frequency during the period averaged 4.7/1000 live births, but continually rose from 3.1/1000 in 1980 to 6.4/1000 in 1994. The increase, related to the use of echocardiography beginning in the 1990s, was almost entirely due to the more than doubling of ventricular septal defect, the most common defect, two-thirds of which were classed as small, from 1.1/1000 in 1980-4 to 2.0/1000 in 1990-4; while several of the other more common ones (atrial septal defect, ostium secundum, etc.) hardly changed in frequency. Patent ductus arteriosus in premature babies was omitted.

Associated noncardiac malformations, over one-third chromosomal in origin, occurred in 26% of cases; discounting which reduced the overall frequency during the period to a mean of 3.5/1000 live births. The chromosomal conditions were not named, but it can be safely assumed that most were Down syndrome, and that of the otherwise rare atrioventricular septal defect they were responsible for most of the two-thirds of the 5% they comprised of all defects. Surprisingly few stillbirths were registered. Epidemiological details will be discussed below.

The follow-up report concerned births in 1980-2000, but aside from this lengthier survey, the outcomes were hardly different from the earlier one (Bosi et al. 2003). The frequency again increased more or less continually over this extended period, from 3.1/1000 births to 7.5/1000 births; which was mostly if not entirely due to increased ventricular and to a much lesser extent atrial septal defect discovery, which together formed the major part of all. Aside from these defects, the remainder were fairly stable, fluctuating between about 0.5-1.0/1000 during these years. Again a large fraction, 24%, were associated defects and of these 38% were chromosomal anomalies and Down syndome three-quarters of the latter.

A tanatalizing finding of this survey was that the frequency of atrioventricular septal defect, usually a rare condition, increased 2.5-fold from 1.6/1000 in 1980 to 4.1/1000 in 2000, whether of the complete, the incomplete, or both forms of the condition was not specified. Since the defect is many times more frequent than this in Down syndrome, as described below, the great increase–generously assuming it was of the complete form–could have been due either to an explosion in the occurrrence of Down syndrome or to expansion in its ascertainment. Although a high level of Down syndrome was found in the district in which the described survey was conducted (Cocchi et al. 1982), no report has been discovered of a dramatic increase in it. It is probable therefore that once again recent use of sensitive means of diagnosis, identifying less severe degrees of the defect, was the basis of the much increased detection.

A combined report of numerous European malformation registries noted an overall frequency of congenital heart disease, not all structural, in infants in 1980-4 of 4.2/1000 total births, 21.9/1000 in stillbirths and 4.2/1000 in livebirths; of the total number 1.3% were in induced abortions and 3.7% in stillbirths (Anon. 1987). The most common was ventricular septal defect, comprising 32% of the total at 1.42/1000 births, which along with most defects remained constant in these years. Atrioventricular septal defect, the form again undescribed, was seen in 0.16/1000 births and 4.4% of all defects.

A later report noted an increased frequency in infants, 4.8/1000 births, but varying greatly, from 1.7/1000 in some areas to 9.9/1000 in others (Anon. 1994a). Of the overall figure livebirths accounted for 90%, induced abortions following prenatal diagnosis 6%, and stillbirths 4%. Although the report was reluctant to assign responsibility for this wide variation, there can be little doubt that the major reasons, as hinted in the earlier publication, were style and quality of ascertainment and diagnosis, which varied from country to country. Supporting this supposition it was also noted that areas where the ventricular septal defect frequency was highest were

those in which small such defects, i.e. those most likely to be underdiagnosed, were most common (Pexieder et al. 1995).

A registry in the Marseille area ascertained congenital cardiovascular and other malformations in all livebirths, stillbirths, and induced abortions in 1984-90 (Julian-Reynier et al. 1994). The total rate of isolated cardiovascular malformations was 5.3/1000 births, which accounted for 48% of all isolated congenital defects. Few further details were given, the study being focused on examining the impact of prenatal diagnosis on prevalence at birth; for a discussion of which see below.

A congenital malformation registry in southeastern Poland recorded cardiovascular malformations in the several days following birth in 2002-4 of the 12 most severe types of defect of 1.7/1000 births (Górska-Kot et al.), similar to that found in the analysis by Pradat et al. (1993) of the same assortment of defects.

In the French county of Indre-et-Loire, in infants born in 1991-4, a high frequency of cardiovascular malformations of 9.8/1000 was found, by the use of what was termed the new technologies of echo- and Doppler cardiography (Cloarec et al. 1999). The most common abnormality by far was ventricular septal defect, constituting 65% of all defects, some no doubt large but unstated proportion of which were of the minor degree that hardly warranted being included in the compilation. At the same time, indicating a deficient overview, was the smaller than usual frequency of atrioventricular septal defect, 1.2%, than often discovered by others.

## POPULATION STUDIES ELSEWHERE

What apparently was the first attempt to estimate the frequency of congenital cardiovascular malformations in Australia utilized annual death statistics (Wright et al. 1968). Based on various diagnostic sources regarding children born alive in 1955-64, it was calculated that the frequency in infancy and later childhood was 6.0/1000, over 80% composed of six major conditions. Deaths from cardiovascular malformations accounted for about half of all deaths from congenital malformations, one-third dying by 1 year of age; three defects being especially lethal, transposition of the great vessels, coarctation of the aorta, and tricuspid atresia. This rate was confirmed by a later study in Western Australia based on congenital malformation data gathered by the Health Department for births in 1980-5 (Bower and Stanley 1986). In all births diagnosed by 6 years of age the heart defect frequency was 6.2/1000 with ventricular septal defect being by far the leading anomaly, at 52% of all defects, of the relatively small selection listed.

Another study from Western Australia compared congenital malformations in Aboriginal and non-Aboriginal children born in 1980-7, ascertained from multiple sources diagnosed up to 6 years of age (Bower et al. 1989). Despite the overall congenital malformation incidence being almost identical in both groups, about 3.5%, the frequency of cardiovascular malformations was significantly greater in Aboriginals, 9.7/1000 vs 6.7/1000, and this was true of almost every anomaly type listed, e.g. tetralogy of Fallot 0.83/1000 vs 0.25/1000, ventricular septal defect

5.36/1000 vs 3.47/1000, etc.; no adequate explanation for this matter was given, and the assertion that it was also found earlier was challenged (Lancaster 1989).

## LATER US POPULATION STUDIES

Among the numerous uses the US Collaborative Study has been put to was a wide-ranging prospective evaluation of the frequency of congenital cardiovascular malformations (Mitchell et al. 1971a). This, a study of great "magnitude and duration" in 1959-65, involved over 56,000 randomly selected children, almost equally divided between blacks and nonblacks, in 12 medical centers especially in the eastern US. The children were examined periodically from birth to 11 years of age by various means, clinical evaluation, autopsy, cardiac surgery, and catheterization and angiocardiography or both, which found a frequency of 8.1/1000 births (8.3 in whites 8.0 in blacks), 7.7/1000 live births, 27.5/1000 stillbirths, 73.2/1000 neonatal deaths, and 112.6/1000 postneonatal deaths. The commonest by far was isolated ventricular septal defect, with a frequency of 2.4/1000 births. Trailing behind were pulmonic stenosis, at 0.7/1000, and others of lesser rate.

The overall frequencies were overstated to the extent that they included patients with less serious cardiovascular malformations and cardiovascular malformations associated with malformations of other organ systems, whether syndromic or otherwise. This was true of 30% of all cases, 46% of deaths including stillbirths, and 19% of survivors. A large number of the associated defects, according to information found elsewehere (Sever et al. 1970, Mitchell et al. 1971b), consisted of Down syndrome. When all instances of associated defects were omitted the frequency was reduced to 5.7/1000 births. In all, the most common abnormalities were isolated pulmonic stenosis and patent ductus arteriosus, together consisting of 45% of all defects; whereas in stillbirths the commonest was ventricular septal defect, and in neonatal and postneonatal deaths, isolated preductal coarctation of the aorta and isolated patent ductus arteriosus, respectively. It is pertinent, for purposes that will become evident below, to note that complete artrioventricular septal defect comprised 3.1% of all defects, half in stillbirths and 1st-year mortalities, though its later association with Down syndrome was not mentioned. Regarding mortality in toto, almost 20% of the liveborn died neonatally, 30% by 1 year of age.

A comprehensive exploration was made in Olmsted County, Minnesota of the frequency of congenital cardiovascular malformations with the usual panoply of the current diagnostic resources, cardiological examination, surgery, catheterization and angiocardiography, autopsy reports, and death certificates (Feldt et al. 1971). The frequency in liveborn children from birth to age 4 years and some unstated time beyond, almost all white, in 1950-69, was 5.7/1000 live births. This finding referred to the entire county, but in its main city, Rochester, in which the famed Mayo Clinic is located, the finding was 6.4/1000, while for the county outside the city limits it was 4.7/1000; a difference the authors explained by the lower rate of autopsies in the 'county' residents–autopsies being the most important source

of information–which would imply that the 'city' rate was the truer one. However, deducting those with associated malformations, the city rate becomes 4.3/1000 and the rest of the county 3.7/1000.

The defects were diagnosed in 44% of patients in the 1st week, 51% in the 1st month, and 86% in the 1st year; and the corresponding times of death were 24, 31, and 41%. The most frequent defects were ventricular septal defect, patent ductus arteriosus, and transposition of the great arteries, these being 58% of all; in the majority occurring as single cardiac defects, while associated with noncardiac defects in almost one-third of cases, most frequently with central nervous system, limb, and urogenital malformations. An account of the defects associated with deaths at different ages in infancy was not detailed.

In a concurrent apparently unpublished study referred to in Feldt et al. (1971), of autopsied stillbirths in 1950-69, the rate of cardiovascular defects was 50/1000 live births. An earlier study from the Mayo Clinic (Harris and Steinberg 1954) with similar results indicated that the frequency of congenital heart disease in this locality had been relatively stable over many years.

A long term study began in 1960 in California of the frequency of cardiovascular malformation in children of pregnant women enrolled at the Kaiser Hospital in Oakland. An early report presented general findings in children followed by hospital visits to 5 years of age, with diagnoses confirmed by positive electrocardiogram and x-ray (Yerushalmy 1969). Analyzed by age of diagnosis, the rate on the day of birth was 3.7/1000 live births, by 3 years it was 11.5, and by age 5 was increased slightly, to 11.7. Diagnosis was made at birth in one-third of cases, by 1 month in just over half, and in nearly four-fifths by 3 months. The frequency in neonatal deaths was 7.9%, with 41% of deaths occurring in the 1st week. Findings regarding the relation of prematurity to the defects will be discussed below.

A detailed and corrected report followed (Hoffman and Christianson 1978). The diagnosis of cardiovascular malformations was based on physician and special examination and cardiac surgery or catheterization. What was termed the "crude" frequency was determined to be 8.6/1000 live births for "definite" congenital defect, and that diagnosed through follow-up to 5-13 years of age was 9.1/1000 live births. The disease was suspected at birth in 3.3/1000 observed children, and increased progressively with age, to 4.0/1000 at 6 days, 5.2/1000 at 1 month, and 7.8/1000, in 88%, by 1 year. In autopsied late fetal deaths and stillbirths the frequency was 77/1000. Severe noncardiac defects and Down syndrome occurred in an appreciable proportion of the children, and if they are excluded the overall frequency drops to 4.1/1000. In both still- and livebirths by far the most frequent lesion was ventricular septal defect, which suggested to the authors that this anomaly was not the basis of death, a supposition seemingly supported by the defect causing little fetal difficulty.

Comment must be made about the Down syndrome data: its rate in this cohort was 1.94/1000 live births, rather larger than the 1.03/1000 found later in California, even at a time when prenatal screening and termination of pregnancies with Down syndrome were increasing (Hahn and Shaw 1993). This possible discrepancy may indicate a disproportionate level of older women among the group, who as is well

known bear an increased frequency of Down syndrome offspring. This may be evidence of the fact that women enrolling in the study were older than of average age, a detail not mentioned; but perhaps of no consequence, since there is no firm evidence of maternal age having an effect on the frequency of congenital cardiovascular malformations.

The frequency of 9.1/1000 (10.8/1000 if possible cases are included) was larger than found in other intensive studies (5.7-8.5/1000) quoted by the the authors, perhaps because cases with minimal defects were included. These high rates were the outcome of an intensive search, with those suspected of having heart disease undergoing further physical, surgical, and catheter examination to exclude or confirm the diagnosis; such that minimal degrees of morphology, on the borderline of 'normality,' were perhaps included. To my recollection I have not seen this aspect of congenital heart anomalies discussed elsewhere, namely whether there may not be cardiovascular morphological traits that so grade into the normal that they should not be grouped with qualitative deviants, and not considered malformations.

Children with cardiovascular malformations born in Dallas county in 1971-84 were identified by various means and diagnosed by the usual clinical and investigative procedures or autopsy, including a relatively small number by echocardiography, and followed for up to 17 years (Fixler et al. 1990). The total frequency was 6.6/1000 live births, that for severe defects was 3.2/1000. Ethnic groups differed, the overall rate for whites was significantly greater, 7.2/1000, than for blacks, 5.6/1000, or Mexican-Americans 5.9/1000; but this was largely due to minor defects, with severe ones not differing significantly. There was a year by year upward trend of all defects from about 5/1000 in 1970 to about 8/1000 in 1984; largely due to the increase in number of cases with minor forms of ventricular septal defects.

What seems to be the final report regarding cardiovascular malformations from the Atlanta birth defects registry was a brief summary of the findings regarding births in 1968-97 (Botto et al. 2001). It noted that the overall frequency of cardiovascular malformations in terminated pregnancies, stillbirths, and live births diagnosed up to 1 year of age, was 6.2/1000 births, but that in the last 3 years of the survey it increased, to 9/1000; in which time ventricular and atrioventricular septal defects and pulmonary stenosis increased, while transposition of the great vessels decreased.

The frequencies, associations, and other circumstances of cardiovascular malformations recorded in the registries of three regions of the world were compared; all three will be discussed here (Pradat et al. 2003). These were a California regional population-based registry, the Central-Eastern France regional registry, and a Swedish national registry. Children born from the early 1980s to early 1990s had total frequencies of cardiovascular malformations discovered in late fetal life to 1 year of age respectively of 3.2, 2.9, and 2.5/1000 births, statistically significantly different from one another. The frequencies of a set of 12 major cardiac malformations, however, were very similar to one another, at about 1.4/1000, surprisingly small relative to many other studies of children of this age. Which may have been the consequence of excluding identified chromosomal anomalies and less severe defects. It thus seems that the inter-regional variability

stemmed from the different defects collected, mainly regarding the less severe abnormalities, which comprised about half the total.

A noteworthy finding of this study, which otherwise discovered little new, was that cardiac and noncardiac malformations were associated far less often in France and Sweden, 23 and 16% respectively, than in California, 52%, the latter due to many less severe heart defects being included. It was in the second part of the analysis that most of the basis of the differences among the regions was revealed, the frequency of chromosomal anomalies (Harris et al. 2003). This too varied greatly in the three areas, paralleling the overall ones. Thus, while the association with Down syndrome, as usual the commonent, was almost identical in France and Sweden, at about 0.28/1000 births, it was much greater, for whatever reason, in California, 0.46/1000. And the same was true of the other most frequent chromosomal disorders, Edward and Patau syndromes. Which serves to emphasize that an estimate of the baseline of cardiovascular malformations, those to be considered most intrinsic, by which studies are to be more equitably compared, can only be arrived at by excluding associated defects.

The distribution of selected heart defects was examined in births in 1986-99 in racial and ethnic groups in Hawaii (Forrester and Merz 2004). This was enabled through the local birth defects program which received information from multiple sources. The overall heart defect frequency was 17.7/1000 live births, fetal deaths, and terminations. This unrealistically large rate was to a great extent the result of a preponderant fraction being ventricular septal defects, many no doubt with no medical significance. Some defects occurred significantly more often in whites than in other racial/ethnic groups (Ebstein's anomaly, coarctation of the aorta), and the reverse was so for a number of others (tetralogy of Fallot, etc.).

CHAPTER 9

# HOSPITAL-BASED STUDIES

## INTRODUCTION

Putting population studies of cardiovascular malformations into perspective are hospital-based studies of defects found in neonates, sometimes followed up for some months or years. Their focus was the usually smaller but significant proportion of the total of defects, those that are expressed initially and are perhaps the most severe, many before being eliminated and lost to ascertainment by death in early life. Such studies are of two sorts, those that examine the frequency of all congenital malformations or are devoted to particular ones alone. The latter because of their concentrated interest may be expected to produce more accurate estimates of frequency and provide information about types and associations as well. Studies of this sort will be dealt with more or less chronologically.

## EARLIEST STUDIES

The earliest studies were of the former sort, inquiring into the frequency of all congenital malformations. The very earliest one identified concerned births in 1923–32 in the Liverpool Maternity Hospital (Malpas 1937). Congenital cardiac disease was noted in 0.76/1000 births, or 7% of all malformed, obviously a great undercount; perhaps due to only newborn children being considered, although that restriction was not explicitly noted, and to insufficient skill or attention given in detecting covert illness; the latter supposition confirmed by the finding of an acceptable frequency of 1.4/1000 for a readily diagnosed state, Down syndrome.

Another early investigation of congenital malformations generally, in neonates born at the Boston Lying-in Hospital, in 1930–41 noted a frequency of those of the cardiovascular system of 2.2/1000 total births, 2.5/1000 in stillbirths, and 31/1000 in neonatal deaths (Stevenson et al. 1950). About 0.52/1000 births had Down syndrome, clearly an underestimate, and excluding those probably with heart anomalies reduces the overall rate to 2.0/1000. Typical of general studies, heart defect types were not stated. During several spring months in the years surveyed an increased frequency of rubella had occurred, at a time when the teratogenicity

of the virus was still unknown. An analysis of the records, unbiased because of this ignorance, suggested a relation between the disease and congenital defects, but one not further looked into it seems.

In a study directed specifically at congenital heart defects, infants born in the Columbia-Presbyterian Medical Center in New York City in 1946–53, were examined in the 1st week of life with follow-up at 6 and 12 months of age (Richards et al. 1955). The overall frequency in single births over 500 g birthweight, with almost all deaths autopsied, was 8.0, 17.5, 104.2, and 5.6/1000 in all births, stillbirths, neonatal deaths, and liveborns surviving 1 month respectively; the last, high though it may seem, may still have been an underestimate because it did not include those failing to develop symptoms during the 1st year. A little over one-third of the cases had noncardiac malformations, including four with Down syndrome and three with neural tube defects, excluding which reduced the overall frequency to 6.1/1000. There were two instances of common atrioventricular septal defect, neither in Down syndrome. The most frequent abnormality again was ventricular septal defect and an unusually high level of tetralogy of Fallot. The difference in frequency of defects between sexes and between whites and blacks was unimpressive. There was a significant difference however between the premature and the full term, but only in the liveborn, the frequency in the former being three times that in the latter, raising the usual conundrum of the chicken or the egg. An appendix listed details regarding the defects, cardiac and extracardiac, etc., in all cases. The study thus provided a comprehensive appraisal of a serious pediatric and developmental problem, and set the pattern for similar ones to come.

A more limited study of live births in 1952–5 in hospitals in Brooklyn, New York used charts to investigate congenital malformations present in the neonatal period, which revealed a frequency of congenital heart defects of 1.0/1000 livebirths, 0.85/1000 with Down syndrome excluded, the relatively low frequency probably due to inadequate chart recording (Shapiro et al. 1958).

The focus of a study at the London Obstetric Hospital were systolic murmurs in children born alive in 1948–56 and subsequently found to have heart defects (Benson et al. 1961). The frequency discovered over the follow-up period of more than 6 years was 3.6/1000; but actually was probably higher, since some children with such defects do not have murmurs in the neonatal period. Just over half the defects were discovered in the 1st week. Almost half the children died during follow-up period, the great majority in the 1st year.

A limited but detailed study was made of congenital malformations in neonates born in 1965–7 in the Western General Hospital in Edinburgh (Stewart et al. 1969). The frequency of cardiac anomalies, diagnosed upon clinical evidence or by catheterization and angiography, was 2.8/1000 live births. Over half of the relatively small number of affected infants died neonatally, a larger proportion even than that of central nervous system malformations, most with transposition of the great vessels. Stillbirths born at the same time were not described.

## A SIGNIFICANT JAPANESE STUDY

Major congenital malformations in infants born in 1948–54 in three Japanese cities were surveyed in connection with the Genetics Program of the US Atomic Bomb Casualty Commission (Neel 1958). Neonates were examined by a midwife and then a physician within 10 days of birth. In these cases the frequency of heart defects, of unnoted types, was 1.6/1000 live births. In a sample of children reexamined at 8–10 months of age the frequency was 4.5/1000. This figure when augmented by the frequency in perinatal deaths (extrapolated from the Hiroshima data), 0.9/1000, gives the approximate total in infancy of 5.4/1000 total births. A surprisingly small proportion of the cases were associated with noncardiac major defects, including Down syndrome. It is worth quoting the author to the effect that "the diagnosis of congenital heart disease at birth is notoriously unreliable . . . from the findings at nine months there can be no doubt many cases were missed . . ."

The absence from this study of a detailed description of malformation types leaves uncertain the likeness of the distribution to that of other Asian or Asian-descended population; e.g. to American Indians, who had a distribution different in some respects from other ethnic groups (Anderson 1977), but not a dissimilar overall frequency at birth, 4/1000 (Adams and Niswander 1968).

A study of Inuit, who are also of Asian origin, found a frequency of congenital malformations in births in Arctic Quebec and Baffin Island in 1989–94 higher with respect to almost all types (Arbour et al. 2004). Very frequent were heart defects, at 22.9/1000 births, with ventricular and atrial septal defects being especially common. Life style was suspected as causative.

## SCANDINAVIAN STUDIES

A study in Denmark of cardiovascular malformations diagnosed in 1963–73 in children from birth to age 15, as recorded in pediatric and cardiological hospital records and death certificates, found a frequency of the defects of 6.1/1000 children, with 63% detected in the 1st year of life (Laursen 1980). The diagnoses were made by x-ray, auscultation, and electrocardiogram, as well as heart catheterization and autopsy, with mean age of detection of about 2 years. The frequency of the defects increased during the latter years surveyed, mainly through increased inclusion of less severe defects, especially of the most common of the defects, ventricular septal defects, patent ductus arteriosus, and atrial septal defect, indicated particularly by the lower mortality rate during this period. Deaths from associated noncardiac congenital malformations occurred in 13% of the mortalities, omitting which reduced the overall frequency to 5.8/1000. Indicating a hereditary factor was the finding of congenital heart disease in 2.3% of sibs, the largest percentage with fibroelastosis plus cardiomyopathy. Additional etiological matters are discussed below.

A study in Norway was particularly directed at the association of significant noncardiac malformations with cardiac ones, as recorded in the university hospital

in Oslo (Eskedal et al. 2004). In 1990–9 congenital cardiovascular malformation was diagnosed by echocardiography, cardiac catheterization, and in surgery or autopsy in about 7.8/1000 births. Almost one-fifth of cases had an associated noncardiac abnormality, nearly one-third Down syndrome, the second most common gastrointestinal malformations, and a wide assortment of others.

## OTHER EUROPEAN STUDIES

Children 2–15 months old born alive in Leiden, the Netherlands in 1958 were referred to the University Children's Hospital by local physicians or screened by the author and examined by cardiac catheterization, angiocardiography, and sometimes autopsy (Kerrebijn 1966). A wide variety of cardiovascular malformations was found, mostly ventricular septal defect, with a frequency of 8.2/1000 live births. Extrapolating from these findings, it was estimated that one-third of Dutch children 0–14 years old with such defects die in the 1st week of life, half within the 1st month, and 80% by the 1st year. "The proportion of the total infant mortality attributable to these malformations has increased from 7.6% in 1951 to 13.7% in 1962," along with the decrease during this period in the rate of infant mortality.

A study in Paris of malformations registered neonatally in births in 1978–82 found a frequency of cardiovascular malformations of 3.1/1000 total births, being 16.5% of all malformations recorded (Goujard et al. 1983). A significant annual increase in cardiovascular malformations occurred over this short period, from 2.3/1000 in 1978 to 4.2/1000 in 1982; for which no explanation was seemingly offered, but of course was probably related to better ascertainment. It is difficult to see how this could explain the great increase in Down syndrome, from 0.53/1000 to 1.21/1000.

The risk factors involved in a study of congenital heart disease made in Strasbourg and region are reported elsewhere in this work (Stoll et al. 1989). Here basic facts are outlined. Consecutive pregnancies in 1979–86 in maternity hospitals in the region were examined and cardiovascular malformations diagnosed in stillbirths and livebirths followed up for 1 year in 7.6/1000 total births, one-quarter were diagnosed at birth and two-thirds in the perinatal period. Diagnoses were by echocardiography, with or without cardiac catheterization, and autopsy. Three-quarters of the defects were isolated and the remainder associated with noncardiac ones, syndromic or otherwise. The commonest defects were ventricular and atrial septal defects, constituting two-thirds of all. Of the rare condition atrioventricular septal defect, which comprised 3.3% of all defects, over 70% occurred in chromosomal syndromes, of which over 60% were Down syndrome.

## NORTH AMERICAN STUDIES

Data regarding cardiovascular as well as all other malformations, in infants under 1 year of age in births in Iowa in 1963, were obtained predominantly from obstetrical and pediatric hospital records (Hay 1971). The frequency of all congenital malformations was 98.2/1000 total births, almost all live births. Of these, not surprisingly,

only a small fraction, 20%, i.e., 19.6/1000, were major malformations, the remainder minor and "insignificant." The most common of the major malformations were cardiovascular ones, with a total frequency of 4.0/1000, two and a half times as much as neural tube defects. A detailed listing of the cardiovascular defects showed that the commonest of the many specified defects were ventricular septal defect and tetralogy of Fallot, which totaled however only 17% of all defects. Atrioventricular septal defect was not mentioned, but was probably the most frequent defect in the 13% of Down syndrome cases with associated cardiovascular malformations.

In Ontario the frequency of structural cardiovascular malformations in live births in 1975 was 2.7/1000 and of severe cases 1.5/1000. These figures were gathered through data obtained from the cardiology units of several hospitals, in a report of the impact of specialty centers on neonatal heart disease, and lacking certain details were almost certainly underestimates (Cook et al. 1978).

The advance in the treatment and management of heart malformations in the Toronto Hospital for Sick Children was evaluated by comparing the change between 1965 and 1976 in the profile of defects in neonates (Izukawa et al. 1979). The only significant change that occurred during these years was in the relative frequency of patent ductus arteriosus, rising to first place in the order of defects, and seven times more frequent than it had been. The reason for which, as was admitted, was the increased number of premature infants, who often have the condition; and thus that the increased level of the defect was due simply to the better survival of premature infants.

Numerous aspects of congenital cardiovascular malformations in infants born in 1969–74 in all hospitals in New England were described in detail (Fyler et al. 1980). Several data are of most importance here. The frequency of children with heart disease discovered in the 1st year of life was 2.1/1000 live births, confirmed in the majority of cases by clinical observation alone, in most of the others by catheterization. Overall, the most frequent defects were ventricular septal defect, transposition of the aorta, tetralogy of Fallot, coarctation of the great arteries, and hypoplstic left heart syndrome, which accounted for half of the defects.

The overall infant mortality was 40%, regardless of treatment, the gravest risk factors being birthweight below 2.0 kg and associated severe extracardiac anomalies, though whether death was due to the risk factors alone was unclear. The most lethal was hypoplastic left heart syndrome with almost 100% mortality, and the least was ventricular septal defect with about 10% mortality. Associated defects of a wide variety were present in 28% of cases, including different organ systems, syndromes, and chromosomal anomalies.

A long ongoing collaborative effort of five mid-Atlantic pediatric cardiology centers, known as the Baltimore-Washington Infant Study, in its initial report described enrolled infants born alive in 1981–2 (Ferencz et al. 1985). Diagnosis of cardiovascular malformations in the 1st year of life, in addition to the usual invasive methods, catheterization, cardiac surgery, or autopsy, was made by echocardiography, a fairly new noninvasive procedure. The total frequency of major structural defects was 3.7/1000 livebirths, 64% of which consisted of mild defects, "lesser

anatomic abnormalities," detected by the invasive procedure. The only information imparted regarding associated noncardiac defects, and that only indirectly, was that three-quarters of the cases with atrioventricular septal defect (the second most common abnormality after ventricular septal defect) occurred in children with Down syndrome. Omitting the latter cases reduced the overall frequency to 3.4/1000.

A lengthier survey, from 1981–8, gave fuller details regarding one of the original findings, the increase in lesser defects, especially membranous ventricular septal defect (Wilson et al. 1993). The mean overall frequency of cardiovascular malformations during this interval, confirming the previous finding, was 3.6/1000 live births. The rate steadily rose however from 2.7/1000 in 1981 to 6.7/1000 in 1988, the increase limited to defects diagnosed by echocardiography.

Still further details regarding ventricular septal defect findings were given in a subsequent report (Lewis et al. 1996). It noted that the frequency of the defect in infants born alive in 1981–9 diagnosed before 1 year of age was 1.6/1000, about 84% isolated and 16% associated with other cardiac and noncardiac malformations. The overall frequency continually increased, reaching 2.1/1000 in 1989, with the growing use of echocardiography as the primary method of diagnosis. The increase was entirely due to the detection of small defects, in particular of the membranous portion of the septum, comprising about two-thirds of all the defects, which rose from less than 1/1000 births in 1981 to almost 9/1000 births in 1989, while the frequency of moderate size ones remained steady or even decreased. The data regarding spontaneous closure of the defect were incomplete, but in those infants diagnosed from birth to 3 months of age about half of the muscular defects were closed by 1 year, while about one-fifth of membranous ones closed. Discussion of the findings related to sex, race, birthweight, gestational age, etc. will be attended to below.

The association of cardiac and noncardiac malformations was considered further elsewhere (Ferencz et al. 1987). The frequency of noncardiac malformations in infants with cardiovascular malformations was compared with that in randomly chosen controls; information regarding which had been supplied by mothers who selected from a list of "major anomalies" those that occurred in their children. The comparison revealed that many but not all of the noncardiac malformations were more frequent in the cases than in the controls, which according to the authors "demonstrates etiologically meaningful associations," as well as "chance co-occurrences." Neither explanation was further explored.

Two matters need to be considered before these associations can be examined, first regarding the composition of the control group, and second the spectrum of the noncardiac malformations. As for the first, it is clear that the choice of the control sample could not have been entirely random, since none of the controls had an isolated heart defect; such children must have been omitted. Further, one asks whether the proper controls were chosen for the task of comparison. Should not the controls, like the cases, have possessed a class of reference malformations whose association with nonreference malformations was to be examined?

Second, we consider the makeup of the associated malformations individually: chromosomal, syndromic, and nonsyndromic. About 12% of cases but only 0.13% of controls had chromosomal abnormalities, a supersignificant difference. Considered in the context of all births in the period surveyed, the frequency of these abnormalities in the cases was 0.51/1000 live births, and in the controls 0.005/1000; both very low, and even in the former extraordinarily low, compared with previous findings (Kalter and Warkany 1983, Rösch and Steinbicker 2002). The most common of these abnormalities in the cases, three-quarters of them, were Down syndrome, of which there were none in the controls. Even the overall case frequency (taking into account that about one-third of Down syndrome have cardiac defects), 0.59/1000 live births, is significantly less than noted in many studies (Lilienfeld 1969, Anon. 1994b).

As to the next category, syndromic and heritable disorders, in toto 5% of cases and 0.6% of controls had such conditions. Many of what were included in this category however, by any definition, are not and do not include major congenital malformations, e.g. carnitine deficiency, fetal anemia, albinism, antitrypsin deficiency, hypokalemic alkalosis, sickle cell anemia, etc., etc. Additionally the most frequent condition here, in both cases and controls, was polydactly, which is not usually considered a major abnormality; it is also important to recall that it occurs ten or more times as often in black than white babies (Shapiro et al. 1958, Altemus and Ferguson 1965, Chung and Myrianthopoulos 1968, Erickson 1976), and thus its great prevalence was probaly due to one-third of both the case and control babies being black (Rubin et al. 1985); but in addition, when it occurs in blacks, it is usually a relatively trivial defect, "an extra finger being attached to the proximal phalanx of the fifth finger" (Warkany 1971, p. 40). All in all, therefore, the polydactyly and the others not entailing malformations should be omitted from the comparison; this done reduces the overall frequency to 0.14/1000 live births in the cases, and 0.008/1000 in the controls, obviously, on its face, a very significant difference. It is difficult to understand however that a dozen or more individually rare hereditary malformation syndromes would congregate in so relatively small a number of cases. Beyond that, no rationale can be imagined for their association with congenital cardiovascular malformations, and none was offered by the authors.

Last are the nonsyndromic malformations, some of which again are disputable. Omitting which reduces their frequency to 0.24/1000 live births in the cases and to 0.04/1000 in the controls. The former is about what is expected, but the latter falls far short of this. Again there was no discussion by the authors of these facts.

Returning to the matter of the total frequency of cardiovascular malformations discovered in the Baltimore study, this was reported to have increased year by year over the course of the survey (Rubin et al. 1987). But when severe and other defects were considered separately, only the 'other' defects were found to have done so while that of severe ones remained fairly stable. This was attributed to the increasing use of two-dimensional echocardiography; but the defects accounting for the increase were not detailed (see Wilson et al. 1993 for some such details).

The total frequency of 4.1/1000 was constituted of 1.6/1000 severe and 2.5/1000 other, i.e., 61% were not severe. And finally, as was often found by others, mentioned elsewhere in this work, infants with cardiovascular malformations, especially certain ones, had reduced birthweight and a greater prevalence of preterm birth (Rosenthal et al. 1991). Regarding the last, an exception were those with ventricular septal and atrioventricular septal defect. In another study, while the frequency of low birthweight was increased, the prevalence of prematurity was not (Kramer et al. 1990).

What appeared to be the final general report from this long ongoing Baltimore-Washington study focused on the matter of infant death of those with cardiovascular malformations (Kuehl et al. 1999). It found that 18% died during this time, a large proportion in the 1st days or weeks of life. As determined by a community search of death certificates 10% of them died before the heart disease was diagnosed; and in about one-quarter of early neonatal death the malformation was not identified before death. Comparing defects in mortalities and survivors, it was found that atrioventricular septal defect was almost twice as common in the former as in the latter. The attributes found associated with death of children with this defect were prematurity, intrauterine growth retardation, and multiple malformations.

To move on, children born alive in northern and central Alberta in 1981–4 were diagnosed in the 1st year of life by pediatric cardiologists using echocardiography, catheterization, cardiac surgery, autopsy, the same "entry criteria" used in the Baltimore-Washington and other studies (Grabitz et al. 1988). The overall frequency, i.e. as determined by all the methods, was 5.5/1000, and by invasive ones alone, i.e. of mild defects, 3.4/1000. Why did this program find a significantly higher overall frequency than the Baltimore-Washington one, 5.5/1000 vs 3.7/1000, despite both using the same array of diagnostic tools? Comparing frequencies of malformation types gives a possible explanation: the largest difference being the almost doubled frequency of minor forms of ventricular septal defect; perhaps due to overzealous inclusion.

An estimate was made of the frequency of a selection of ten congenital cardiovascular malformations in infants born alive in Louisiana in 1988–9 (Storch and Mannick 1992). Pediatric and surgical records of heart conditions diagnosed in infants by echocardiography, catheterization and/or autopsy indicated the frequency to be 2.2/1000 live births; this excluded cases with trisomy 13 and 18 and Down syndrome except those with atrioventricular canal defect. This relatively low rate, of the commonest cardiovascular malformations, despite diagnosis by modern, sensitive means of detection, compared with contemporary findings, appears to indicate inadequate ascertainment. A higher frequency of some of the defects was said to have occurred in white than black infants, but the indecipherable means of presenting the data made independent examination of this conclusion impossible.

A study at the Boston Brigham and Women's Hospital in 1972–4 and 1979–90 identified congenital cardiovascular malformations in elective terminations, stillbirths, and neonates (Lin et al. 1999). By various but not well described means an overall frequency was found of 3.3/1000 births (not including patent ductus

arteriosus, patent foramen ovale, where deemed physiologic, and some minor defects), 2.7/1000 livebirths, 0.41/1000 terminations, and 0.22/1000 stillbirths. Data regarding individual defects, however, was not imparted. During the interval surveyed the total frequency increased, from a mean of 2.7/1000 earlier to one of 3.7/1000 later, which was entirely due to an increase in the number of terminations, since the frequency in still- and live births was relatively stable. When adjusted by omitting the associated conditions the frequency was reduced to 2.4/1000 births. Omitting Down syndrome cases had the further benefit of removing the effect of advanced maternal age, of which there was some evidence in this study.

The question of how effectively critical cardiovascular malformations can be spotted in asymptomatic newborns was the focus of a program in Albany, New York (Koppel et al. 2003). It was conducted in 1998–9 and entailed examination by oximetry of over 11,000 asymptomatic infants just before discharge from hospital. The defects screened for were a limited set of anomalies deemed detectable by this method. Detected was a frequency of 0.26/1000; and this was considered a success, as judged against the findings of conditions included in the New York State screening program.

## OTHER NON-EUROPEAN STUDIES

It is of interest to consider how many congenital malformations are recognized in the delivery rooms and newborn wards of hospitals in different parts of the world. This question was the focus of a study of births in Israeli hospitals in 1959–60 (Halevi 1967). The overall frequency in all births was 13.2/1000 (69.2/1000 in still- and 12.4/1000 in live births); these figures are slight overestimates since they include several defects of a minor nature. Of all defects those of the cardiovascular system comprised 9.7%, or 1.4/1000 births. The answer, in this study, is that in the 4–5 days in hospital after birth the discovered malformation frequency, for various reasons, was perhaps half or less of the one a complete survey would detect; and the same fraction was more or less true of cardiovascular malformations.

A comprehensive study of the frequency of congenital malformations was made in consecutively born infants in a teaching hospital in Melbourne in 1971–4 (Drew et al. 1977). Disregarding certain genital and limb defects considered by the authors (e.g. hypospadias, undescended testis, dislocated hip), the commonest defects were those of the heart and great vessels, at 5.4/1000, equaling 20% of all defects. The most frequent, as usual, was ventricular septal defect, at 47% of all cardiovascular malformations, and one of the rarest was atrioventricular defect, at 1.8%. As to mortality, 37% and 100% of these two defects respectively perished neonatally.

A study in two other regions of Australia reported on cardiovascular malformations diagnosed during the 1st year of life in children born in 1981–4, with nearly complete ascertainment (Kidd et al. 1993). Diagnosis, made by various means, found an overall frequency of 4.3/1000 live births, very near that found in Melbourne, slightly more than one-third in the 1st week and nearly 90% before 6 months. Almost half consisted of ventricular septal defect and left-sided

obstructive lesions, such as hypoplastic left heart syndrome, coarctation of the aorta, and aortic stenosis. Almost one-quarter were associated with noncardiac defects, including recognized syndromes and chromosomal defects, three-quarters of the last being Down syndrome. Not surprisingly Down syndrome was heavily associated with atrioventricular septal defects, which were more frequent that usual, being 6.1% of all defects and 2.1/1000 births. The frequency of isolated defects therefore was 3.2/1000. About 12.5% of infants were preterm, and about 16% low birthweight, which is about twice and three times the usual respectively. The relation of cardiovascular malformations to various epidemiological variables was considered, including maternal age, ethnicity, etc. This subject will be discussed below.

A survey of the records of all hospital births in the Northland region of New Zealand in 1966–77 found a heart defect frequency of 1.46/1000 births diagnosed in hospital, of which the great majority were isolated, but the types not enumerated (Hanify et al. 1980). A register established in New Zealand in 1978 received data about children with congenital cardiovascular malformations diagnosed before 1 year of age, passively ascertained from routinely collected official data (Borman et al. 1987). These multiple sources, mostly hospital and mortality and autopsy records, gave a frequency of cardiovascular malformations of 3.5/1000 livebirths. The most common anomalies ascertained from hospital admission records were ventricular septal defects (of a lower frequency than found elsewhere; some unknown proportion of which were admitted to be not of the serious type requiring surgery), transposition of the great vessels, patent ductus arteriosus, and coarctation of the aorta, these alone accounting for half of all the defects; but from mortality reports the most common were hypoplastic left heart syndrome and common truncus defects. The numerous factors making for probable underascertainment were discussed.

Records of live births in 1986–8 in the major maternity hospital in Singapore revealed a heart defect frequency of 1.74/1000 neonates, the most common being ventricular septal defect, at 0.49/1000 (Thein et al. 1992). In this area, therefore, with a multiethnic society of over 90% Chinese and Malays, the heart defect frequency at birth was similar to that in other parts of the world, comprising just 11.5% of all defects, this because musculoskeletal and gastrointestinal defects it seems, were more common and nervous system defects less so than they usually are elsewhere.

An apparently far larger frequency was diagnosed in Chinese neonates born alive in 1987–9 in a large hospital serving Hong Kong and its region (Sung et al. 1991). Cross-sectional and Doppler echocardiography detected cardiovascular malformations at or soon after birth in 6.4/1000 live births. Multiple defects are alluded to but not enumerated. The most frequent defect, as in most studies, occidental or oriental, was ventricular septal defect, at 3.0/1000 births, or 47% of all defects; the large number perhaps due to including minor, inconsequential types of the defect, but no mention was made of that possibility. As elsewhere, atrioventricular septal defect was one of the scarcest, at 2.2% of all defects or 0.14/1000 births. Down syndrome was mentioned only in one of a number of autopsied early postnatal deaths, this one with tetralogy of Fallot.

A later report from the same Hong Kong hospital was concerned with several hundred Chinese children 4 years old and younger with symptomatic cardiac defects seen in 1994–5 (Jacobs et al. 2000). While the distribution of defects was similar to that in western populations, tetralogy of Fallot and pulmonary stenosis seemed more common while aortic stenosis and hypoplastic left ventricle less common. As noted elsewhere in this work, the commonest defects in Down syndrome patients were ventricular and atrioventricular septal defects, at 38% and 25% respectively, the reverse of the usual pattern in western studies.

## BRITISH STUDIES

Infants born in Newcastle upon Tyne in the early 1990s were clinically examined for cardiac malformations at various times during the 1st year of life and diagnoses confirmed by electrocardiography (Gregory et al. 1999). Malformations were recognized in 3.2/1000 live births, 14% before 6–8 weeks of age. The importance of this study is not particularly in the frequency of the defects that were found, especially as the study protocol is all but unanalyzable, but in the fact that the frequency declined rapidly with age at diagnosis, while the assortment of defects found at the different times was not greatly dissimilar.

A retrospective review was made of heart malformations in infants up to 1 year of age ("because most clinically significant heart disease will have presented by this age") born alive in 1987–94 in the UK northern health region, the diagnosis confirmed by echocardiography, cardiac catheterization, surgery, or necropsy (Wren et al. 1999). The number discovered by echocardiography alone was not noted. The total frequency was 5.3/1000 live births, but omitting preterm births, associated noncardiac malformations, etc. reduced it to 4.8/1000, and omission of patent ductus arteriosus associated with significant preterm birth reduced it further, to 4.1/1000. Only 45% of those with cardiovascular malformations were considered abnormal on neonatal examination. Most frequent were ventricular septal defect, pulmonary valve stenosis, coarctation of aorta, tetralogy of Fallot, and transposition of great vessel, together comprising 64% of the total; but again the least common were most lethal: hypoplastic left heart, common arterial trunk, interrupted aortic arch, complete atrioventricular septal defect, and pulmonary stenosis, which comprised 16% of the total, but 47% of the fatalities. Later prospective studies yielded a higher frequency ("almost all of which is accounted for by the detection of more small ventricular septal defects"). An instructive item dealt with the assortment of cardiovascular malformations in the cases of Down syndrome, 25% with ventricular septal defects, but as usual most with complete atrioventricular septal defect, 48%.

A later study in the same region, of live births in 1985–97, examined changes over time in prevalence of cardiovascular malformations discovered in the 1st year of life (Wren et al. 2000). The frequency of all cardiovascular malformations over the entire period was 5.6/1000; and the only significant secular increase was of minor defects, mainly small ventricular septal defects, no doubt due to increasing use of noninvasive methdology.

A most recent report from this region dealt with the frequency of cardiovascular malformations in preterm infants born in 1987–2001 (Tanner et al. 2005). All liveborn children suspected of having cardiovascular malformations during the 1st year of life were referred to a single pediatric cardiology unit. The total load of cardiovascular malformations was 5.7/1000 (excluding atrial septal defect and patent ductus arteriosus), approximating that found in this area earlier (Wren et al. 1999, 2000). In those assumed to be preterm, 7.3% of all liveborn, the frequency was 12.5/1000, over twice that in term infants, 5.1/1000. The excess was not explained by a greater frequency of minor defects, but was partly explained by an increase in preterm births in children with Down syndrome with complete atrioventicular septal defect. The finding in children with Down syndrome will be discussed below.

As was stated many pages earlier, it is taken as a verity that cardiovascular malformations are present at birth, as the term 'congenital' indicates. However, since such conditions are almost entirely asymptomatic in the newborn, the frequency of cardiovascular malformations as detected at that age has been a matter of uncertainty. From early on heart murmurs were taken as indicating their presence. The question, three-quarters of century later, still remains rather unresolved it seems; but a recent study has helped in alleviating this.

The meaning of cardiac murmurs in neonates was determined in babies born alive at term in 1995–6 in a large district hospital in Newcastle upon Tyne (Ainsworth et al. 1999). Babies were routinely examined within 48 h of delivery to detect the presence of cardiac murmurs, and 0.6% found to have a murmur (the exact same figure found on death certificates in Philadelphia by Murphy in 1947). Infants with a murmur were usually soon reexamined by echocardiogram, and a structural heart defect confirmed in about half of them (3.5/1000), 60% with ventricular septal and a variety of other defects. Further examination before the age of 1 year detected an additional number with cardiovascular malformations, none of whom had murmurs at birth, bringing the total to 7.9/1000. This high level resulted from including many small ventricular septal defects, detected as usual by the early echocardiography.

A rather different outcome was found in a prospective trial in 1994–8 at the Royal Maternity Hospital in Belfast (Sands et al. 2002). Its purpose was to test the efficacy of early diagnosis in detecting cardiovascular malformations in the neonatal period. The study was conducted as follows. While still in hospital the infants of women randomized before delivery were either scanned echocardiographically or examined by clinical assessment, the latter considered the controls. In the former significant cardiovascular malformations were detected in 25.4/1000 and in the latter 10.4/1000 controls.

As based on frequency of all defects, the difference was not due to excess of any particular defect; e.g. ventricular septal defects made up about one-third of all defects in both groups. But basing the outcome on the fraction in each group told a different story. Again using ventricular septal defects as the example, the frequency was 8.6/1000 in the scanned group and 3.5/1000 in the controls. Hence, while

early echocardiography appeared to give a more complete diagnosis, the greater frequency in the cases was in all probability due to detection by the sensitive device of some unknown number of smaller, less severe instances of this defect; whose omission brought the findings in line with those of other studies. A difference between cases and controls was not true of all defects, however, since the overall frequency of the relatively rare atrioventricular septal defect was 0.41/1000 in both groups.

CHAPTER 10

# CARDIOVASCULAR MALFORMATIONS AND BIRTHWEIGHT

As early as the middle of the 20th century heart defects were noted to be related to birthweight. For example, Richards et al. (1955) found a significant difference between premature and full term babies, the frequency in the former being three times that in the latter, and many others had the same experience. In one instance though there was a demurral, Landtman and Hjelt (1959) noting that while one-third of cases weighed less than 2500 g, the same was true of all autopsied children at that period. Most others agreed however that premature offspring, i.e. those under 2500 g birthweight, were more often affected that those of greater weight (e.g. Smithells 1968, Usher and McLean 1974, Fyler et al. 1980, Rubin et al. 1987, Berry et al. 1987, Rosenthal et al. 1991, Kidd et al. 1993).

But was this propensity due to retarded fetal growth or too early delivery? The question of whether or to what extent it resides in immaturity or prematurity is a perplexing one. Only with respect to ventricular septal defect have I found any attempt to face the challenge, and only a small number of articles were identified that plumbed the problem.

Observation of children in hospitals in New York City in 1960–3 found isolated ventricular septal defect in 0.95/1000 term infants and in 4.52/1000 live births in offspring of less than 2500 g birthweight; a significant increase considered to be in accord with the increased frequency of congenital defects generally in premature infants (Hoffman and Rudolph 1965).

The Collaborative Study, mentioned several times elsewhere in this work, collected a relatively small number of instances of isolated ventricular septal defect in over 50,000 births in 1959–65 (Mitchell et al. 1967). Prematurity was almost three times as frequent in the cases as in a comparison group; and over twice as many died as did those with other heart defects. But as well as being of lower birthweight, they were also of lower gestational age. Both questions were thus addressed but not separated.

One investigator attempted to unravel this matter (Yerushalmy 1969). In considering each factor by itself it was found that children weighing 2500 g or less at birth had an overall malformation rate about three times that of heavier ones; and that though the contrast was not so great, those born at less than 37 weeks of pregnancy

had almost twice the rate of those born at 37 weeks or more. But the most telling contrast was in conjoining these factors in the attempt to disjoin them. Comparing offspring of 1501–2500 g born at less than 37 weeks with those born at 37 weeks or more, the respective rates were 17.8 and 39.4/1000 births, i.e. a relative rate of 2.2; meaning that prematurity was of greater consequence in this regard than immaturity. And the same was true, but of lesser degree, in newborns of 2500 g or more, with a relative rate of 1.5.

An effect was also found of very low birthweight on death rate of children with heart defects. In a hospital in Queensland, Australia in all children born in 1988–99 it was 13%, in those of 1000 g or less significantly greater, 26%, than in those of 1000–1500 g, 5% (Kecskes and Cartwright 2002). Despite this profound difference the two groups had almost identical heart defect rates, 3% and 2%. With respect to death of the malformed ones, the 'ultralight' surprisingly had a rate half that of the others, 6% vs 12%, the difference was not statistically significant however. One significant death rate difference was seen in the babies labeled as intrauterine growth retarded, with those retarded some four times more frequently defective than those not.

The most common defects (excluding atrial septal defect, minor pulmonary stenosis, and patent ductus arteriosus) were ventricular septal defect, 53%, and coarctation of the aorta, 17%. But surprisingly rare, it would seem for dead malformed offspring, was atrioventricular septal defect, at 1.8%; whether it occurred in the one with dysmorphic features that had Down syndrome was not stated. Of the affected ones 40% died, most had coarctation, none ventricular septal defect. As was true of most such reports the defects in the dead and not dead were not listed separately, not permitting some insight into the basis of the possible differences.

One report, concerning children ascertained in an Atlanta population survey in 1970–84, listed cardiovascular defects and their frequencies individually, in this instance in intrauterine growth retarded children (Khoury et al. 1988). It found that 28% of all children with heart defects were growth retarded; with a range from 17% for transposition of the great vessels to 34% for tetralogy of Fallot. As might be expected, lethality was closely associated with severity, which is part of being multiply malformed. It is no surprise therefore that with few exceptions all the defects were associated ones, and that only isolated atrial septal defect and hypoplastic left heart syndrome were not related to growth retardation.

CHAPTER 11

# PATENT DUCTUS ARTERIOSUS AND BIRTHWEIGHT

The story of persistent or patent ductus arteriosus is fascinating. The ductus arteriosus, as we know, is a fetal blood vessel that conducts blood from the right ventricle to the descending aorta, and coincident with other changes in the circulation that take place at birth, it undergoes a closing process within days after that time; the process by which this happens is not of concern here. In some number of infants this process fails and the duct remains open. How often this happens and under what circumstances and conditions it happens will now be discussed.

Patent ductus arteriosus was often noted in the articles reviewed for this work; e.g. in the early population study in Toronto of children of ages from birth to 15 years its frequency was 0.25/1000 (Gardiner and Keith 1951). The difficulty with most notices of the condition is that salient details, the affected childrens' age and birthweight and whether the defect was isolated or not, were not mentioned. Some of this information was provided in a report from Birmingham, that the frequency of the isolated defect in newborns was 0.31/1000, that it comprised 13% of all affected newborns, and that 90% of instances of the defect were isolated (MacMahon et al. 1953).

Other studies, older and newer, reported the same numbers, more or less. In Sweden in 1941–60 0.60/1000 had the defect, all isolated, 19% of all defects, 39% males; it was present in 8% of mortalities, most of them early neonatal deaths (Carlgren 1959, 1969). In a clinical study in 1953–7 in Toronto 2% of newborns had the defect (Rowe and Cleary 1960). In a San Francisco cardiac registry the defect was identified in 0.19/1000 school children, 10% of all defects (Mustacchi et al. 1963). In Baltimore 9% of neonatal deaths had the defect (Mehrizi et al. 1964). In a Liverpool population registry 0.36/1000 had the defect, one-third dying in early childhood (Hay 1966). In Buffalo 2.4% of neonatal autopsies had the defect (Lambert et al. 1966).

In Helsinki in 1947–70 the defect was seen in 7% of neonatal deaths, 33% male (Landtman 1971). In Minnesota in 1950–69 0.59/1000 livebirths had the defect, 15% of all defects; in a rare instance the role of birthweight was acknowledged, 21% being premature (Feldt et al. 1971). In the Collaborative Study 0.62/1000 newborns had the isolated defect, 31% of neonatal and infant deaths (Mitchell et al. 1971a). In Budapest in 1963–5 0.74/1000 births had the isolated defect, 44% male,

31% dead neonatally (Czeizel et al. 1972). In Sweden in 1961–70 the defect was the dominant or contributing cause of death in 3.6% of infant deaths (Esscher et al. 1975). In Liverpool in 1960–9 the defect was found in 0.65/1000 births, 35% male, 15% dead neonatally (Kenna et al. 1975). In Blackpool in 1957–71 0.38/1000 total births had the isolated defect (Bound and Logan 1977). In the Kaiser study in California in 1959–66 0.52/1000 livebirths had the defect, 6% of all defects (Hoffman and Christianson 1978).

Later in Toronto a great increase in the defect as a percent of all defects was noted, being 8% in 1965 and 31% in 1975, due to increased survival of premature infants, another of the seldom references to this fact (Izukawa et al. 1979). A bit further south, in New England, strangely virtually no increase occurred in the frequency of the defect in about the same years, 0.135/1000 live births in 1969–74 and 0.141/1000 in 1975–7; as for birthweight, 10% of cases weighed less than 2500 g and 3.4% more than 2500 g (Fyler et al. 1980). In the Liverpool population in 1960–9 it was found in 0.65/1000 livebirths, with no further details (Dickinson et al. 1981).

A very low rate, 0.09/1000, without explanation, was found in the mid-Atlantic region in 1981–2 (Ferencz et al. 1985). In the same region in 1981–4 the defect occurred in 2.6% of multiply affected infants and 2.1% of those with isolated defects (Ferencz et al. 1987). A national register in New Zealand in 1978 found the defect in 0.41/1000 livebirths (Borman et al. 1987). In a study of many European registries the mean rate of the defect in births in 1980–4 was 0.18/1000, 4.8% of the total defects (Anon. 1987). In Swedish births in 1981 the defect was seen in 11.3% and 1.8% of all liveborn children with heart defects under 2500 g and greater than 2500 g birthweight respectively (Carlgren et al. 1987). In Alberta in 1981–4 the rate was 0.25/1000 livebirths, 4.5% of all defects and 0.19/1000, 5.8% of all defects, in those noninvasively or invasively diagnosed respectively (Grabitz et al. 1988). In Dallas county in 1971–84 the defect was seen in 0.35/1000 livebirths or 5.3% of all defects (Fixler et al. 1989).

In 1981–4 in areas of Australia the defect was seen in 0.12/1000 live births delivered at greater than 36 weeks of gestation, or 3.4% of all defects (Kidd et al. 1993). The defect was seen in the northern UK health region in 1987–94 in 0.27/1000 births, 5.1% of all defects, of which 2.5% died in infancy (Wren et al. 1999). In Emilia-Romagna in 1980–2000 the defect occurred in 0.11/1000 live births, 53% isolated (Bosi et al. 2003). A note of interest: patent ductus arteriosus was not mentioned in stillbirths in any of the numerous reports reviewed (Hoffman 1987). Review articles gave the frequency of the isolated defect as 1 per 2500 to 5000 births in the normal population (Cassels et al. 1975, Rowe 1978).

Many other estimates were larger. The above summary shows the population frequency for the most part was about 0.60–0.70/1000 births, i.e. 1 per 1400–1650. The few facts provided indicated that the great majority were isolated. Its concurrence with some other heart defects was discussed in detail by Cassels et al. (1975). The general impression however is that the population load of this defect did not vary over the earliest years and in various parts of the world.

It was known early that females were more often affected than males (Rowe 1978), as was reported in the small number of studies summarized above in which the subject was mentioned, where the ratio was mostly about 1 male to 2 females. Like other malformations with sex ratio imbalances, e.g. oral clefts and neural tube defects, this requires developmental explanation, based on multifactorial analysis (e.g. Fraser 1976). The only external agencies known to impinge on its frequency are race and rubella, which will be considered elsewhere. Another, prematurity, will be discussed here.

Interest in the connection between prematurity and patent ductus arteriosus began with the discovery in the late 1950s that the ductus often remained open in premature infants with respiratory distress syndrome. This was confirmed in the next several years, and then given quantitative reality by finding the highest frequency in births of 1500–1999 g, with a lesser one in still lower weights explained by death before the usual age of diagnosis (Neal et al. 1975). The connection was put on a firm basis by the report of the nationwide increase in the reported frequency of the isolated, but not the complex, form of the defect, in various parts of the US (Anon. 1975, Anderson et al. 1978).

In Atlanta, where the increase was closely analyzed, there had been a "consistent, sustained, upward trend" in this frequency, from 0.70/1000 live births in 1968 to 3.2/1000 in 1975 (Anderson et al. 1978). The explanation of this trend clearly was its connection to low birthweight. This was made obvious by the ever-increasing proportion, year by year, of cases in babies weighing less than 1500 g at birth, rising from 25% in 1968–9 to 54% in 1974–5. Looking at the total for the entire period, a direct relation with weight was present, the percentage soaring from 0.4/1000 livebirths in those of 2500 g or more, to 51/1000 in 1000–1499 g group. But no clear, hard explanation of this rise was ventured: though the defect was more frequent in blacks than whites, in large hospitals than smaller ones, in western mountain states than elsewhere, etc, none fitted the data well; only that physician awareness may have been responsible for much of the increase.

But again there arises the question of the nature of the weight insufficiency the defect was associated with, whether it was due to retarded prenatal growth or to early birth. This matter was examined in babies consecutively born in 1972 in a Los Angeles hospital (Siassi et al. 1976). A strong relation was found to birthweight, three times as many affected in those of 2000 g or less than in the 2000–2500 g group. But the defect was also strongly related to gestational age, almost four times as many affected in those of 28–30 weeks as of 34–36 weeks.

The relative influence of weight vs age was explored by comparing the lighter-weight babies who were of appropriate size for gestational age with those small for gestational age, and finding that 43% of the former were affected and 5% of the latter; thus while both these subgroups had virtually identical birthweight, those of lesser gestational age had the larger defect frequency, indicating that immaturity rather than prematurity was the major factor determining the defect; in which interpretation the above outlined Atlanta study concurred.

This is where the story of significance to this work essentially comes to an end; only to be added is a note that recent efforts have focused on means of inducing ligation of the duct by sugical and pharmacological means (Malviya et al. 2003).

See below for the relation of paternt ductus arteriosus and altitude.

CHAPTER 12

# CARDIOVASCULAR MALFORMATION AND MORTALITY

## INTRODUCTION

For most of the 20th century congenital heart malformation was associated with high rates of infant mortality, greater than for almost any other malformation type. Thus in the US in 1910 the death rate associated with heart defects was 1.74/1000 live births (Anon. 1913). It was similarly high in England and Wales, being 1.5–2.0/1000 live births in 1912–67, the rate being fairly constant throughout this span (Rogers and Morris 1971). In California in births in 1957–61 the rate was 1.68/1000 live births (Allen 1968). In Sweden in births in 1961–70 the rate of infant death from cardiovascular malformation was 1.33/1000 livebirths (Esscher et al. 1975).

Only toward the end of the century was the rate moderated, down in the US to 1.06/1000 live births by 1980 and to 0.59/1000 live births by 1995, a significant overall reduction during these years of 44% (Anon. 1998). The greatest change was for ventricular septal defect, which was reduced 61%, for transposition of the great vessels the reduction was 36%, and much less so for hypoplastic left heart syndrome, down 5%. A similar decrease at the end of the century was seen in statistics from Canada, which showed an infant mortality rate from heart defects of 1.04/1000 live births in 1981–3 and 0.73/1000 in 1993–5 (Wen et al. 2000). Yet the latter report noted that the fraction of all lethal malformations in infancy attributed to heart defects apparently increased from 35.7% to 37.1%, comprising in the latter period 37% of all lethal defects.

This means that in the first decade of the 20th century death from heart defects comprised about 3.5% of all deaths from malformations, while in the last decade it was about 15%. Thus relative to all malformation deaths those from heart defects had about quadrupled; which perhaps means, at least in part, that prevention of deaths from this source had been less successful than for malformations generally.

Another way of looking at the record is by proportion of neonates with heart defects that die young. A roll call follows. Estimates made in Birmingham in 1940–4 reckoned 40% dead by 1 year, the majority in the 1st week (MacMahon et al. 1953), the same rate as seen in New York in 1946–53 (Richards et al. 1955). In Liverpool in 1960–4 30% of births with heart defects died young (Hay 1966). An

early Swedish report gave it as 31% dead in 1st year, almost half in 1st week (Carlgren 1959). The rather wide variations in these early findings prompted the question of why, was it that appreciable numbers were being missed at birth or was there a failure of later recognition? Carlgren (1969) puzzled that "in spite of improved general infant care . . . mortality had not greatly decreased..being about the same in 1961–65 . . . as in 1941–50."

In Rochester, Minnesota in 1950–69 24% of infants with heart defects died in the 1st week and 41% in the 1st year (Feldt et al. 1971). In Liverpool of births with heart defects in 1961–9 about 18% died neonatally (Kenna et al. 1975). In California 8% of stillbirths had heart defects and 13% of livebirths with heart defects died neonatally and a similar percentage died in infancy or later (Hoffman and Chrtistianson 1978). In Toronto better surgery and postoperative care were credited with the improved record, survival after the 1st month rising from 37% in 1965 to 70% in 1975 (Izukawa et al. 1979). In Sweden 21% of infants born in 1981 diagnosed with heart defects died in infancy (Carlgren et al. 1987).

In Newcastle 17% of children with heart defects born in 1985–90 died in infancy, 70% of them neonatally and 85% in the first 4 months (Abu-Harb et al. 1994). These deaths comprised 43% of all deaths due to congenital malformations and 90% of the total infant mortality. A further report from Newcastle of births in 1987–94 found 17% of heart defect children dead by 1 year (Wren et al. 1999).

A Swedish report of births in 1981–6, gave evidence of the importance of the source of data, whether the difference between them was real or not: a cardiac registry noted that 31% of offspring with heart defects died within 7 days of birth, while a malformation registry gave the rate as 75% of stillbirths and neonatal deaths (Pradat 1992a).

It is reasonable to believe that some of these deaths are to be attributed to the seriousness of the conditions, especially when combined with noncardiac defects. Death associated with low birthweight, maternal age, etc. are considered elsewhere (See Ferencz et al. 1997, pp 351–4 for a discussion of birthweight and heart defects). Studies of heart abnormalities in mortalities thus provide augmented information about the frequency of cardiovascular defects, the types that are prone to earliest elimination, the age at which this happens, and about the noncardiac defects they may be associated with.

## CARDIOVASCULAR MALFORMATION IN ABORTION

Studies reviewed here begin with cardiovascular malformations found in abortions and then for the most part in autopsied early mortalities. Findings in mortalities in more generalized studies are mostly presented elsewhere in this work (also e.g. see Hoffman and Christianson 1978).

The frequency of congenital malformations is larger in spontaneous abortions than in newborn children, which clearly means that some malformed embryos and fetuses are eliminated before birth (Warkany 1971, pp 38–41, 1978). Consequently, to arrive at full knowledge of the frequency of malformations, those in embryos and

fetuses that do not reach birth must also be taken into account. For malformations such as cardiovascular ones, whose prenatal identification may require special measures, the task of establishing this full number is at least as difficult as it is to do postnatally, as some of the following descriptions will show.

Hertig and Sheldon (1943), in a former time, established criteria for distinguishing between induced and spontaneous abortions. Both denote termination of a pregnancy before the fetus is viable, which at present is considered to be around the 20th week of gestation. In considering the frequency of malformations in spontaneous abortion this age limitation must be remembered. This is relevant because some prenatal studies described below included conceptuses older than the accepted age limit. [As an aside, the term 'spontaneous,' which in medicine means 'not-induced,' even as a convention is inappropriate; numerous causes of such events have been identified (Hertig and Sheldon et al. 1943, Rushton 1985).]

With respect to malformations, spontaneous abortions are not likely to be typical of all conceptuses, since whatever causes their death may distort their malformation picture; nor may even so-called therapeutic abortions, i.e. those performed for medical reasons, be devoid of distorting features (Miller and Poland 1971). Consequently only by examining unselected embryos and fetuses may the 'true' prenatal frequency of malformations in general and of particular types hope to be revealed. Unselectedness however may be nearly impossible to achieve, bias sometimes being unwitting; and even in the most favorable circumstances not allow total discovery.

## CARDIOVASCULAR MALFORMATION IN INDUCED ABORTION

The means of obtaining embryos for study untainted by conceivable distortions are limited by human imagination, hence rather few have been examined (noninvasive procedures for such estimation, and their limitations are discussed below). A possible way of realizing this goal, on the face of it, was perhaps reached in post-world war II Japan through the agency of the Eugenic Protection Law of 1952. This allowed abortions to be induced mainly for socioeconomic, i.e. nonmedical, reasons; but of these too one must be wary, since e.g. most of them were done in middle class individuals of somewhat advanced maternal age (Nishimura 1975).

Taking advantage of the law, a considerable number of "virtually unselected" (to use the authors' term) induced abortions were examined. The first study was devoted to externally observable abnormalities, thus excluding cardiovascular ones, in 3–10 week old subjects, with the discovery generally of higher frequencies than occur in newborn infants (Nishimura 1969, Nishimura et al. 1966, 1968). A later and closer inspection found cardiovascular malformations, in 50/1000 externally normal embryos of 6–8 weeks of age (Takano et al. 1976). An extraordinarily large proportion, three-quarters of them, were ventricular septal defects, some no doubt artifacts due to delayed closure of the septum.

More detailed reports noted cardiovascular malformations in 12/1000 5–6 week old specimens and 35/1000 in 6–7 week old ones (Nishimura 1975, Semba 1975) and overall in a larger sample, 35/1000 (Nishimura et al. 1987), 25 times as

common as in Japanese newborns. The most numerous defects were persistent atrioventricular canal (i.e. atrioventricular septal defect) and ventricular septum defect. The most significant result was the finding that most, but not all, of the comparatively common types of cardiovascular malformations were those also seen in newborn infants. Thus the frequency of malformations in induced abortions, even at early stages of embryonic life, as in spontaneous ones, as will be seen below, increased with advancing development (Nishimura et al. 1968).

It seems intuitive that a more accurate estimate of the 'real' frequency or variety of malformations may be found in induced than in spontaneous abortions, regardless of the imperfections of ascertainment and inadequacies of examination of the former. Substantiating this supposition by comparing spontaneous and induced abortions is difficult however, simply because induced ones in good condition have been relatively unavailable. The only extant data to my knowledge that are of help in deciding this matter revealed a larger frequency of malformations generally in the former, as intuition foretold, in one case over six times greater, and of selected malformations, almost three times greater (Miller and Poland 1971, Gal 1973). Even so, frequencies in induced abortions still exceeded the 'natural one,' something not easily explained.

## CARDIOVASCULAR MALFORMATION IN SPONTANEOUS ABORTION

A matter introduced above, that of associated malformations, may be of even greater pertinence in considering the prenatal frequency of cardiovascular malformations, since abortions are very often multiply malformed. The topic will therefore need especial attention.

The vast bulk of the earliest studies of spontaneous abortion dealt with those occurring in the first weeks of pregnancy, whose condition seldom allowed for analysis of localized maldevelopment (Hertig et al. 1959, Stratford 1970). Others were uninformative regarding cardiovascular malformations, since they dealt only or nearly so with externally observable abnormalities (Stevenson et al. 1959, Sentrakul and Potter 1966, Poland and Lowry 1974); and this was sometimes true of induced abortions as well (Nishimura et al. 1966). One study of chromosomally normal embryos and fetuses of a wide range of age noted an exstrophic heart but no other cardiovascular defect (Singh and Carr 1967).

Some proved more fruitful. The first in a series of reports from hospitals in British Columbia, in a relatively small number of nonselected spontaneous abortions under 22 weeks of gestation, noted a frequency of anomalies of specific systems of 27/1000, among which were a small number of unspecified cardiovascular anomalies, but only in younger ones (Poland 1968). In a larger sample of the same ages the overall frequency was 20/1000 (Miller and Poland 1970).

In spontaneous abortions, of 10–20 weeks of age, collected in 1973–4, the overall cardiovascular malformation frequency was 88/1000; but the defects were present only in specimens of less than about 13 weeks of age, with a frequency of 250/1000

(Yasuda and Poland 1975). Thus, in these specimens, as was true of earlier observations, the frequency fell off suddenly beyond a certain age; the possible explanation offered for which was progressive elimination of defective ones. The commonest type was ventricular septal defect, always associated with other cardiac defects, which would support that supposition.

The findings in nearly 2000 conceptuses spontaneously aborted before 20 weeks of pregnancy collected in 1966–76 were described in detail by a Vancouver group (Poland et al. 1981). Almost two-thirds of the abortions were embryos, i.e. less than 10 weeks of age, the great majority growth disorganized. Of the others 11% had systemic defects, and 3% of these were single heart defects, but of sorts not considered malformations. In the fetuses, those 10–20 weeks old, 40.5% had a variety of defects, cardiovascular ones being 19.4% of them all (79/1000), many associated with other defects. Detailed listings showed isolated ventricular septal defect to be the most common one, not including atrioventricular septal defect. Various epidemiological associations will be discussed below. The defects found in fetuses were very similar to those seen in live term offspring reported in a British Columbia registry, but in greatly reduced numbers in term offspring, and this was markedly true of heart defect.

Since the most important morphogenetic cardiac processess in human fetuses are complete by about 7 weeks of age (according to Chuaqui and Bersch 1972), most major cardiovascular malformations should be detectable in fetuses, especially since the fetal heart resists the maceration that occurs in utero after death. The puzzling matter was broached of what is responsible for the death of fetuses with cardiovascular malformations, which in themselves are not thought to be incompatible with uterine life. The possible answer lies in the lethality of defect multiplicity, which occurred in about half the affected fetuses.

Study of spontaneous abortion had a long history in the Central Laboratory for Human Embryology at the University of Washington. The first report of its activities concerned embryos and fetuses with various types of localized malformations aged 2 to over 19 weeks obtained from local hospitals over a 7-year period (Nelson et al. 1971). Among the defects in the formed embryos and fetuses were two of the heart, an atrial and a ventricular septal defect, at 9–13 and greater than 19 weeks respectively, for a very low frequency of 2.4/1000. During the next 7 years a larger number was found, giving a frequency of 5.3/1000 (Fantel et al. 1980). Another paper did not mention cardiovascular malformations at all (Shepard et al. 1988).

Two further reports were apparently the final ones from this laboratory. One dealt with specimens obtained in 1977–8 that were at 9–40 weeks of gestational age, composed therefore of both spontaneous abortions and stillbirths (Chinn et al. 1989). The total frequency of cardiovascular malformations was an unrealistic 130/1000, but the findings were not separated by age and tabulated data were incomplete. Thus as a contribution to knowledge of the frequency of cardiovascular malformations in spontaneous abortuses the report is without merit.

The second, apparently a summarization of 20 years of study, noted findings in a large number of specimens of a wide range of gestational ages, 16 to over 270 days, this time conveniently presented by age (Shepard et al. 1989). The frequency of cardiovascular defects in those 2–18 weeks old (i.e. spontaneous abortions) was 11.5/1000 and in older ones (stillbirths) 47.6/1000, perhaps explaining the unrealistic one noted above. It may be mentioned as an aside that although this laboratory noted that it collected many induced abortions, these were never described, a wasted resource it would seem. It may also be remarked that another function of this laboratory was monitoring abortions as indicators of fetal hazards of environmental origin, and the interesting finding in that respect was recorded that no change in overall malformation frequency was detected in the years the laboratory was engaged in that project.

A high frequency of cardiovascular defects was found in a detailed examination of spontaneous abortions mostly under 24 weeks of gestation collected in several hospitals in Leeds in 1975–83 (Gerlis 1985). The overall frequency, 15.4%, progressively decreased with fetal age, from 33% in those 10 weeks or under to 9.5% in those older than 20 weeks, without an explanation of the decrease. Omitting the last, technically not stillbirths, and those with noncardiac defects, the overall frequency was still 178/1000. More than three-quarters of the defective fetuses had ventricular septal defects, in almost all associated with various other cardiac defects, and in addition associated noncardiac defects occurred in about one quarter of cases. It bears noting that a mere 1.8% had atrioventicular septal defects, in opposition to the sizable number with other defects.

It is difficult to reconcile the finding in the youngest conceptuses in this study with that in the study of Poland et al. (1981) described above. At this age, the latter authors said, "[I]dentification of a specific defect may be impossible in an embryo . . ." and indeed none were found; whereas in the Gerlis study one-third of such embryos had heart defects. It is useful also to compare the proportion of unexaminable embryos in these two studies: 77% in Vancouver and 20% in Leeds.

No attempt was made by the author to explain the larger than usual overall frequency, but others pointed out some possibilities (Ursell et al. 1985). Though the abortions were said to have been unselected, they may not have been consecutive and hence possibly included special cases; second, some minor defects were admitted, as well as defects not ordinarily considered cardiac defects per se, such as ectopia cordis and acardia.

## PERINATAL PATHOLOGY STUDIES IN THE US

Information about how often children with heart defects die depends on its source. Data from hospitals, public heath records, and broad surveys vary because of the nature of the population considered, some yielding overstated, others minimized findings.

We start with findings in autopsies mostly of perinatal and infant deaths, beginning with an early survey in the University of Minnesota Pathology

Department in 1936–41 (Clawson 1944). Several thousand autopsies were examined, 84% stillbirths and infants (most to 5 months), with the frequency in them respectively of 12 and 51/1000, with no significant sex difference. Most common in both were ventricular septal defect, 26%, alone or combined with others, followed by coarctation of the aorta and transposition of the great vessels. Very rare was atrioventricular septal defect, 0.7% of cases, whose subjects lived 1 month.

A study in the Boston Lying-in Hospital detailed the types of cardiovascular malformations in consecutively autopsied perinatal deaths, about four-fifths stillbirths and early neonatal deaths, in 1931–54 (Ober and Moore 1955). The frequency in these combined was 60/1000, and the most common were transposition of great vessels and large ventricular septal defect, together almost half of all defects. No instance of atrioventricular septal defect was mentioned and only one of Down syndrome. A small number, mostly stillbirths, had multiple noncardiac malformations; but a much larger number had multiple cardiovascular malformations. Thus it seems that the deaths could be blamed on the seriousness and the frequent multiplicity of the cardiac abnormalities and not on their association with noncardiac ones.

The concurrence of cardiac and noncardiac defects in autopsies of ages from stillbirth to 26 years, again unfortunately not separated by age, was the subject of a report from the medical school in Indianapolis (Wiland 1956). Cardiovascular malformations were found in 29/1000 specimens examined in 1926–53, half since 1950, almost one-third also with noncardiac defects. The two commonest anomalies were ventricular and atrial septal defect, at 42% and 24% respectively, and a scarce one, atrioventricular septal defect in 1.5%. One of the latter occurred in one of the four Down syndrome cases. Regarding the various malformation conjunctions the author concluded, as many others did later, that "there was no constant association between a specific extracardiac anomaly and a particular type of congenital heart disease."

In autopsy records of the Johns Hopkins pathology department from 1927–59 the most frequent heart defect in stillbirths as in neonatal deaths was ventricular septal defect, respectively 30% and 17% of all defects, followed by transposition of the great vessels, coarctation of the aorta, and mitral and/or aortic atresia, in all of which the frequency in stillbirths and neonatal deaths was substantially the same, while one of the rarest, atrioventricular septal defect, occurred in 5% of stillbirths and 2% of neonatal deaths (Mehrizi et al. 1964). Almost all those with ventricular septal defects died of causes other than the defect, including associated serious noncardiac defects; while those with transposition died as a result of the defect, near the end of the 1st week. A small number had atrioventricular septal defects, but the one Down syndrome case was free of the defect. Noncardiac malformations occurred in 27% of cases, mostly associated with ventricular septal defect. Differences in the composition of cardiovascular malformations between that found in this study and the two described just above were conjectured to have been due to variations in selection, classification, etc.

A report from the Collaborative Project, described fully above, contained information regarding all malformations in autopsied early mortalities (Froehlich and Fujikura 1969). As usual the most common defects were those of the cardiovascular

system, in both sexes and in whites and blacks. About 3% of births in 1959–64 were stillborn or died neonatally, and the frequency of such malformations, those, as the authors commented, whose development would normally have been completed by the end of the 9th embryonic week, was 38/1000 stillbirths and 79/1000 neonatal deaths, 29% of which in toto were associated with noncardiac defects. The many heart defect types were enumerated, by far the most common ventricular septal defect, which however, was over twice as common in neonatal deaths as in stillbirths, 36 vs 16/1000. One of the ordinarily least frequent defects, atrioventricular septal defect, was slightly more common in stillbirth than neonatal death, 8 vs 6/1000. How many of the few Down syndrome stillbirths and neonatal deaths were so afflicted could not be determined from the data given.

Among defects detected early in the Baltimore-Washington area survey in 1981–4 were those in a relatively small number of autopsies examined in detail (Rubin et al. 1987). Almost all died soon after birth. They had a wide variety of defects, with none predominating, the largest number were of transposition of the great vessels, hypoplastic left heart syndrome, and ventricular septal defect, comprising almost half of all. Of the two Down syndrome one had a atrioventricular septal defect. Comparing frequency of cardiovascular malformations in autopsies and infant survivors, major septal/conotruncal defects and atresias/hypoplasias were more common in the former, while septal and other defects less common. Also more common was birthweight less than 2500 g and associated noncardiac defects of a wide variety of sorts.

## PATHOLOGY STUDIES ELSEWHERE

Informative reports also came from other centers. In the Helsinki Children's Hospital in 1948–57 cardiovascular malformations were found in 86.7/1000 consecutive autopsies of 1 day to 15 years of age, half before the 1st month and 93% before the end of the 1st year (Landtman and Hjelt 1959). The most common defects were transposition of the great vessels, truncus arteriosus, trilocular heart, and ventricular septal defect, which comprised 52% of them all; some of these, it was said, were only rarely found in older surviving individuals with heart disease. A wide variety of noncardiac malformations, often multiple, occurred in 43% of the cases, almost equally urogenital, gastrointestinal, skeletal, and central nervous system. One-third of the cases had a birthweight below 2500 g, which however was about the same as in all chldren autopsied in this period.

A later more detailed study of deaths of children with cardiovascular malformations in the Helsinki Children's Hospital in 1947–70 included etiological details to be discussed further on in this work (Landtman 1971). A morphological appraisal of over 4000 consecutive autopsies of children under 1 year of age found 13.6% to have "definite" congenital malformations of the heart, i.e. upon omission of isolated patent ductus arteriosus and minor aberrations. This frequency continually increased from about 5% in 1947 to about 25% in 1970, which was not explained. That of defects in early and late neonatal deaths was 59.0 and 36.7/1000 autopsied

infant deaths respectively. The commonest defects were ventricular septal defect and transposition of the great vessels, about 13% of all defects in both. Coarctation of the aorta was most lethal, 71% of all occurrences dying neonatally, of ventricular septal defects it was 65%, and of transposition of the great vessels, 48%, etc. A wide variety of serious extracardiac malformations occurred in half of cases under the age of 6 months, none however with an excess frequency. The rare defect, complete atrioventricular septal defect, was seen in 3.3%, often complicated with other cardiovascular malformations, mentioned because of its frequent ocurrence in Down syndrome, to be discussed further below. Down syndrome occurred in 26% of defective cases, exceeded in frequency only by esophageal atresia. A wide-ranging accounting of the findings of overall mortality and of that of specific defects in earlier studies is found in review articles (Campbell 1973, Hoffman 1987).

An analysis of cardiovascular malformations in autopsied material was made in the Hebrew University in a series collected in 1949–59 (Abramovici and Liban 1964). Heart malformations were found in 89/1000 neonatal and 91/1000 postneonatal deaths. The leading defects were ventricular septal defect, coarctation of the aorta, transposition of great vessels, and tetralogy of Fallot; approximately one-third of the cases were associated with noncardiac malformations. A higher frequency occurred in non-Ashkenazi, 11.8%, than Ashkenazi Jews, 6.8%, for which no explanation could be found. The low frequency in stillbirths, 17/1000, was attributed to low autopsy rate. In less than one-quarter of the cases could death be assigned to the heart defect.

In several large Hamburg hospitals the frequency of congenital cardiovascular malformations in autopsied stillbirths in 1948–60 was 1.2/1000 births, i.e. about 15% of all infant deaths with cardiovascular malformations (Hoffheinz et al. 1964). The most frequent were ventricular septal defect and transposition of the great vessels, accounting for about 35% of the total; tetralogy of Fallot and atrial septal defect were the least lethal and transposition most. Association with noncardiac defects was not mentioned.

A review of death statistics in the Uppsala region of Sweden in 1961–70 found cardiovascular malformations the dominant cause of infant deaths, in 1.3/1000 livebirths, approximately one-third dead in the 1st week of life and one-fifth the 1st year (Esscher et al 1975). The most common were mitral and/or aortic valve atresia, ventricular septal defect, and isolated transposition of the great arteries, comprising over one-third of them all. About 55% of the mortalities also had malformations of many other systems, most frequently Down syndrome, the defects in which however were not detailed.

Fragmentary mortality data from Denmark for 1963–73 noted that 25% of affected childen died after 1 month (Laursen 1980). Comparing the overall death rate during the period of the survey, it was found to be 41% lower in the later part, 1969–73, than the earlier, 1963–68, which was true to one extent or another of death from almost all the various defects.

At the pathology institute of the University of Vienna in over 40,000 autopsies made in 1950–69, two-thirds under the age of 1 year, there were 17.6/1000 with

malformations of the heart and great vessels (Bankl 1970). The most frequent were tetralogy of Fallot, complete transposition, and ventricular septal defects, which accounted for just over 40% of the total. Only about one quarter of the defects were isolated, the remainder associated with other heart and noncardiovascular malformations. The frequency of complete artrioventricular septal defect was 4.2%, about two-thirds combined with other defects, most of them probably in Down syndrome.

In the Central Bohemian Region of the former Czechoslovak Republic, a region surrounding but excluding Prague, heart defect was analyzed in all stillbirths and deaths under 15 years of age in 1952–78 (Goetzová and Benesová 1981, Samánek et al. 1985, 1988). Death certificates and autopsy records noted such defects in 20/1000 stillbirths and 74/1000 livebirths (44% dead before age 1 month, 90% before 1 year), comprising 41% of all congenital malformations. A large proportion were associated with noncardiac defects, 12% with Down syndrome. The most common defects were ventricular septal defect, transposition of the great vessels, and hypoplastic left heart syndrome. A detailed account was given of the proportions of the types of cardiovascular malformations occurring in the live- and stillbirths; interestingly several were more common in live- than stillborn children, e.g. complete transposition was almost three times more frequent in the former.

In the then German Democratic Republic in 1979 isolated congenital cardiovascular malformations were seen in 63/1000 stillbirths and 1st year deaths, 37% dying perinatally (Busch et al. 1985). The commonest defects were hypoplastic left heart syndrome, ventricular septal defect, and transposition of the great vessels. An increased frequency of the defects was seen with advancing maternal age, whether related to Down syndrome was not noted, nor in fact was this syndrome mentioned at all.

At the Berlin Institute of Pathology of Humboldt University in autopsies in 1963–83 of children up to 16 years of age 21% had cardiovascular malformations, 20% dying perinatally, over three-quarters in the 1st year (Reinhold-Richter et al. 1987). The most common were atrial and ventricular septal defect, transposition of the great vessels, etc. Extracardiac defects occurred in 7.2%, the most common those of the central nervous system; the malformation syndrome frequency was 5.6% including 1.4% with Down syndrome.

A sequential segmental analysis was used to describe the cardiovascular malformations in autopsied infants dying at less than 1 year of age in several hospitals in the UK in 1974–84 (Hegerty et al. 1985). I do not even make a pretense of understanding this analytical system, but fortunately for the antediluvian reviewer the primary lesions found were listed. Heading the list were complete transposition and a variant of atrioventricular septal defect; but the material being highly selected these and other findings were hardly representative.

A prospective study was made of cardiovascular malformations in Jutland, Denmark in unselected deaths of children aged 0–14 years in 1977–9 (Vesterby et al. 1987). The great majority of the subjects were stillbirths and neonatal deaths, but the malformation frequency was not clearly presented by age. In sum, 22.6% of

autopsied mortalities had congenital cardiovascular malformations, but they were more than twice as common in live- than stillbirths, 27 vs 12%. The most frequent defect, patent ductus arteriosus, is usually omitted from consideration in many studies; excluding it here reduced the overall defect frequency by over half, to 8.9%. The next most frequent were ventricular and atrial septal defects; the rare defect, atrioventricular septal defect, at 1.5%. Down syndrome occurred in 2.0% of the mortalities, and 78% of them had cardiovascular malformations, but the number with this rare defect was not noted. Noncardiac defects occurred in 30% of the cases, almost twice as frequent as in mortalities without cardiovascular malformations. The heart defect was considered the cause of death or the major contributing factor in 82% of the livebirths.

Cardiovascular malformations in infant deaths in 1985–90 in seven northern counties of England can be compared with those in survivors (Abu-Harb et al. 1994). The overall frequency in live births diagnosed during infancy in this interval was 4.6/1000; and in infant mortalities it was 93.5/1000, 70% dead within the 1st month of life. About three-quarters of the defects in mortalities were classed as complex or significant, e.g. endocardial fibroelastosis (a dubious malformation) and hypoplastic left heart syndrome, and were the most lethal ones. Severe noncardiac defects occurred in 16% of the mortalities, about two-thirds of which were chromosomal abnormalities.

Among the specified defects there was an inverse relation between frequency and lethality, e.g. the commonest, ventricular septal defect, one-third of cases, was one of the least frequently associated with lethality, etc. Complete atrioventricular septal defect, often less seldom seen, had a frequency of almost 7.5%; its close association with Down syndrome was proved by its occurring in all such instances with severe noncardiac abnormalities. A finding mentioned almost parenthethically was that a yearly analysis showed that while complex and significant cardiovascular malformations were stable over the years, minor defects increased as "ascertainment improved," a subject whose implications will be discussed below.

It is of much interest that features of congenital cardiovascular malformations in some African populations were similar to those in Europe and North America. Thus, in deaths at unstated ages in 1951–68 in Kampala, Uganda, the rate was 6.4/1000 (Wood et al. 1969); while in infant deaths it was much larger, 52/1000. Although not detailed it is likely that this pertained to death in very early infancy. Twenty percent of all cases had a noncardiac involvement, omitting which reduces the overall rate to 5.1/1000. The most common defects were atrial and ventricular septal defects, while isolated patent ductus arteriosus and coarctation were relatively infrequent. The frequency of various types of defects was thus similar to that in non-Africans; at the same time there were possible intertribal variations, but not detailed.

Similar findings were seen in 1965–70 at the University College Hospital in Abadan, Nigeria, in which a review of necropsy reports was combined with clinical diagnoses using the customary procedures of the day, electrocardiogram, angiocardiography where indicated, and surgery (Antia 1974). Indigenous African children

from birth to 14 years of age had the same pattern and proportions of congenital heart malformations as non-Africans, with ventricular septal defect being the most common type followed by patent ductus arteriosus, atrial septal defect, pulmonary stenosis, and tetralogy of Fallot. Almost half died neonatally, and two-thirds in the 1st year, but the defects associated with age at death were not dertailed. Possible evidence was found of an association between maternal rubella infection and patent ductus arteriosus.

Most recently once more the frequent occurrence of noncardiac malformations in pediatric autopsies with cardiovascular malformations was documented, this time in the university hospital in Ankara, Turkey (Gucer et al. 2005). In autopsies of infants dying in 1977–2002 cardiovascular malformations were found in 92/1000, the commonest was ventricular septal defect; noncardiac malformations were present in 46%, but did not appear to occur nonspecifically, since some cardiovascular malformations were more and others far less often or not at all associated with other abnormalities.

No great summary can be extracted from the entries in this section. As would be expected, where the distinction was drawn, the heart defect frequency was far greater in mortalities than in suvivors; but less expected and less understandable that the frequency was less in stillbirths than in neonatal deaths. Also where comparisons were drawn, defects in mortalities were of more severe and complex types than those in survivors, but no facts were presented to support such a difference between stillbirths and neonatal deaths; nor were there apparent differences between the latter in rate of associated defects.

## CLINIC STUDIES

In a survey of births in the Babies Hospital in New York City in 1946–53 heart defect frequency was 18/1000 in stillbirths and 104/1000 in neonatal deaths, with only a small difference between those below and above 2500 g birthweight (Richards et al. 1955). Both had a variety of cardiovascular malformations, with none apparently predominating; 10% of all defects were patent ductus arteriosus, all liveborn, weight not indicated; another 4% had atrioventricular septal defect, stillborn. The frequency of associated noncardiac malformations was 28% in the former and 40% in the latter, but many of the survivors were also multiply affected. It thus seemed in this sample that being multiply malformed was not especially lethal.

In a Gothenberg study an unrealistically minute percentage of the considerable number of stillbirths had heart defects (Carlgren 1959). Of the postnatal deaths, on the other hand, almost 31% with heart defect died in infancy, 46% in the 1st week, 72% the 1st month.

A study in the Toronto Hospital for Sick Children of infants with cardiovascular malformations dying neonatally in 1953–7, in trying to estimate their frequency, relied on a procedure that in fact defeated that purpose (Rowe and Cleary 1960). Certain of the defects were incredibly more frequent in mortalities than survivors, e.g. aortic atresia or stenosis was over 10 times more common; which was obviously

due to the referral to the hospital of severely sick children from a wide area. On the contrary, other usually common defects, ventricular septal defect, tetralogy of Fallot, and transposition of the great vessels, were about half as frequent as in the survivors. Furthermore, about a quarter of the deaths were premature and resulted from causes other than the heart defect. Another ordinarily infrequent defect, atrioventricular septal defect, was about equally common in both survivors and nonsurvivors. The number of the latter who may have had Down syndrome was not mentioned. The lesson, learned too late, was that "the ideal method is prospective analysis . . ."

Another instance of biased selection presenting a distorted picture was of mortalities with a high frequency of cardiovascular malformations seen in an active cardiac department attracting "seriously ill congenital cardiac patients from a considerable area . . ." (discussion by Webster in Terplan 1953). The department in question was in the Buffalo Children's Hospital, so it may be interesting to look at a later report from this facility (Lambert et al. 1966). The latter reported that the commonest malformations in babies mostly dying neonatally with isolated major cardiac defects in 1949–64 were hypoplastic left heart syndrome and complete transposition of the great vessels. Since aortic atresia, a component of the syndrome, was also the most common defect reported in the Toronto study described in the previous paragraph, this seems to have been taken as corroborating the finding, without considering that in both studies the finding had a biased basis. Because local physicians "commonly refer newborn infants for diagnosis and therapy," the patients were believed to be a "representative group of newborn cardiac patients," while, in actuality, they were not. The observations regarding an amomaly of great interest in this work, atrioventricualar septal defect, may still have provided valid data: 4.2% of 1st month deaths, over 70% of which occurred in the 1st week.

Clinical aspects of death of children with congenital heart defects were not the subject of reports it seems for some time. After a gap of years such deaths were recently described in centers including a hospital in Vestfold County, Norway (Meberg et al. 2000). Of the children born in 1982–96 with such defects, 12% died, half neonatally and almost three quarters before 1 year of age. Comparing the frequencies of the most common defects in all cases with those in mortalities yields information about their relative lethality or other factors. Thus, in distinction to the 59% of all cases that had ventricular septal defects, only 14% of mortalities did so, while for atrial septal defect the two were almost identical, 8% and 7%. The latter situation was true of almost all the others, pulmonary stenosis, patent ductus arteriosus, transposition of the great vessels, coarctation of the aorta, tetralogy of Fallot, but not for two others, atrioventricular septal defect and hypoplastic left heart syndrome, both of which were four to six times more common in deaths than in all births. Of relevance is the fact that lethality was not different in cohorts born in the earlier years of the survey than the later, i.e. the frequency of the severe defects was the same in the period before and after more sophisticated scanning methods came into use.

## POPULATION SURVEYS

Information about the impact of congenital heart defects on mortality as learned from broad studies has been fragmentary over the years. We may begin with studies from California in about the 1960s. A state-wide death certificate study found that approximately two-thirds of deaths attributed to congenital heart disease in 1957–60 occurred in infants, the great majority in the 1st week (Allen 1968). Of those with specified diagnoses, the most frequent were ventricular septal defect, patent ductus arteriosus, atrial septal defect, and transposition, adding up to almost half of all. Although 3.8% of the deaths had Down syndrome, the most frequent of all the associated conditions listed, atrioventricular septal defect was not explicitly mentioned.

An early report concerning heart defects in children of families enrolled in the Kaiser Foundation Health Plan in the San Francisco area included some mortality information (Yeushalmy 1969). Children born alive in 1960–6 had a frequency of heart defects of about 10.8/1000 discovered by continuous observation during the first 5 years of life, only one-third diagnosed at birth. Twenty-two percent died during the observation period, the mortality highest on the day of birth, 9% dying during the 1st week, declining gradually thereafter.

In the multihospital collaborative study, described elsewhere, perinatal and later mortality due to heart defects of various types was described in detail (Mitchell et al. 1971a). In sum, 27.5/1000 stillbirths had heart defects, as did 73.2/1000 neonatal deaths, i.e. over two and a half times as many in the latter as in the former. A far smaller imbalance was true of the commonest defect, that of the ventricular septum, 6.7/1000 vs 8.4/1000. Regarding different defects, generally the commonest ones were least lethal during infancy and vice versa, e.g. 83% of ventricular septal defects survived, while none with coarctation of the aorta did so.

A survey, based on birth and death certificates, was made of midcentury trends in US infant mortality from all causes (Berry et al. 1987). Leading the list in mortality progress in the period surveyed was cardiovascular malformation, whose rate decreased from 1.70/1000 live births in 1960 to 0.98/1000 live births in 1980, and as a proportion of all malformations decreased from 48% to 40%. Analysis by birthweight revealed that while both premature and mature births shared the rate decrease, only in those of 500–2500 g had there been a decrease in the proportion of all malformations, while in heavier births there had hardly been any change. Differences in these matters between white and black births will be discussed below.

In Leicestershire in 1977–85 perinatal mortality fell from 21.0 to 9.5/1000 births, and while deaths from malformations (excluding neural tube defects) remained constant at about 1.8/1000, their contribution to this mortality increased from 10% to 18% (Young and Clarke 1987). Almost 14% of all deaths were due to malformations and 20% of these were from isolated heart defects, and another 18% Down syndrome, many of whom also have heart defects.

A report from a New York State congenital malformation registry described information received in 1983–8 (Druschel et al. 1996). In these years the rate of infant death from malformations decreased, from 74/1000 in 1983 to 64/1000 in

1988 [continuing the phenomenon described above for the entire US population, despite which the percentage of deaths from malformations increased (Berry et al. 1987).] Included among the data concerning deaths from all malformations was a brief mention of the heart. Exceeded only by deaths from a few other categories of malformations, 26% were due to heart defects, for a frequency of 126/1000 infants. No further information was given.

A US nationwide survey of infant deaths from congenital heart disease in 1979–88 reported data from the National Center for Health Statistics and many state birth certificates (Gillum 1994). These sources noted a heart defect mortality rate of 0.71/1000 live births in the 1st year of life, 59% in the 1st month. The most common, in order of frequency, were hypoplastic left heart syndrome, transposition of great vessels, and coarctation of the aorta, which totaled about one-third of all specified defects. Atrioventricular septal defect mortality rate was 0.03/1000 live births. Decline in death from some defects, e.g. transposition of great vessels, atrioventricular septal defect, common truncus, and tetralogy of Fallot, may have been associated with improved surgical technique and intensive care; on the contrary, deaths from hypoplastic left heart syndrome slightly increased in the years reviewed. The usual inadequacies of accuracy and completeness associated with such data collection no doubt pervaded these findings.

Annual reports of the US National Center for Health Statistics were used to examine the trend in the US in the relation between infant mortality and cardiovascular malformation (Lee et al. 2001). The frequency of infant deaths from all such malformations declined 50% in 1970–97, from 1.27 to 0.63/1000 live births. Many of the specified abnormalities followed this pattern, e.g. deaths from atrioventricular septal defect declined 46%; but this was not as true of other types of defect, thus tetralogy of Fallot fell a mere 8%, while others–among them the leading causes of death–hypoplastic left heart syndrome and transposition of the great vessels, rose 20 and 30% respectively, the former proportionately accounting for 20% at the onset of the period and 23% at its end. Considerations regarding these malformations must take into account associated abnormalities, the most frequent Down syndrome, whose frequency during the interval remained constant.

A concurrent report from the US National Center for Health Statistics, of trends and patterns of death from heart defects, based on filed certificates of death of all ages in 1979–97, confirmed many of the findings of the two population studies just described (Boneva et al. 2001). Death due to these defects decreased significantly during the period, declining 39% in infants and 57% in children 1–5 years old, the latter age group nevertheless still had the highest mortality rate.

As for individual defects, most of them–transposition of great vessels, ventricular septal defect, aorta coarctation, atrioventricular septal defect with or without Down syndrome–declined 40–60%, however unequally or unevenly. Others–hypoplastic left heart syndrome and tetralogy of Fallot–declined far less, 8% and 10% respectively; with death sometimes delayed and occurring later. Blacks were still at a disadvantage with respect to some of the defect types, with smaller reductions than in whites, e.g. for hypoplastic left heart syndrome, transposition, etc., despite having

lower frequencies for some of them, with the racial gap–as often noted for other attributes–not getting smaller, again as so often the case, attributed to health care access deficiency and other supposed inadequacies. The authors similarly speculated that the reductions they, and others, have found resulted from improved diagnosis, bettered surgical technique, advances in intensive care, and the like. The persistent difference in racial mortality, they insist, is an indication of unfinished business. Time as usual will tell.

Canadian data tell very much the same story as found in the US (Wen et al. 2000). During 1981–95 infant mortality from cardiovascular anomalies exceeded that from any other congenital malformation, though its impact moderated greatly over this time. The rate of infant death from heart defects declined from 1.04/1000 live births in 1981–3 to 0.63/1000 in 1993–5, a 35% decrease; but nevertheless maintained approximately the same relative position in the causes of all malformations, at about 36–37%. In contrasting this constancy with a finding in earlier years of an increase in time in percent of infant death due to malformations (Goldenberg et al. 1983), the authors failed to consider the role in the earlier period of continued elimination of deaths due to malformation.

A detailed account was given of death in infancy from various heart defects in an American state with a historically poor mortality record (Cleves et al. 2003). A survey of Arkansas registry data showed that 18.5% of malformed children born in 1993–8 had heart defects, and that 11.8% of them died in the 1st year of life, half neonatally. By far most of the deaths were cases of ventricular and atrial septal defects, constituting 85% of all, almost two-fifths occurring neonatally. Death from one of the least common of the malformations, atrioventricular septal defect (4.9% in this sample), as noted by others, occurred less often when associated with Down syndrome, than when not associated, 3.8% vs 11.5%. The proportion of one or more associated heart defects in one versus the other could not explain this difference, because approximately the same proportion was present in both.

## CARDIOVASCULAR MALFORMATION AND CHROMOSOMAL ABNORMALITY

We turn for a moment to an important topic in the study of abortion, that of cytogenetics. In the years following David Carr's (1963, 1965) pioneering discovery of the occurrence and role of chromosomal aberration in abortion, many articles appeared, which described and categorized the aberrations but gave scant attention to the morphological defects associated with them. This was not surprising since most specimens studied chromosomally were very young, consisting of embryonic fragments and early fetuses, which did not lend themselves to the examination of focal abnormalities (Singh and Carr 1967, Mikamo 1970). An early exception was a study of renal and certain other abnormalities in some older abortions with the XO chromosomal composition, the anomaly in the majority of individuals with Turner syndrome (Singh and Carr 1966). Other reports mentioned the occasional occurrence of localized defects, but failed to describe them (e.g. Kalousek et al. 1993).

Among the few that at least in part reported morphological details was a study of a large number of consecutive spontaneous abortions under 28 weeks of age identified in 1977–81 in some New York City hospitals (Byrne et al. 1985). About a quarter of the malformations were cardiovascular; but the only ones specified were those in the specimens with chromosomal anomalies, a fifth of them not abortions but stillbirths. The authors were very liberal in their usage of terms, and 'spontaneous abortion,' 'miscarriage,' and 'early fetal death,' were used interchangeably. The defects thus were all of them of the 'associated' variety.

A further report from this source described the cardiovascular malformations presumably in the same 8–28 week old consecutive spontaneous 'abortuses,' a considerable fraction of which therefore were not abortions (Ursell et al. 1985). Most of the relatively few cardiovascular malformations (ventricular septal defect, tetralogy of Fallot, atrioventricular septal defect) occurred in those less than 20 weeks old, 24.3/1000 total specimens. Three of the five karyotyped ones had nontrisomy chromosomal abnormalities. What abortions with cardiovascular malformations died of was pondered, based on cytogenetic considerations, accepting that many of the specimens included in this category were actually stillbirths. Since the frequency of cardiovascular malformations in chromosomally normal abortions (1.1%) was of the order found in newborn infants, it seems that death was not related to the defectiveness. The connection between isolated cardiovascular malformations and death, as it is with many other types of malformations, therefore remains unclear.

Incidentally, and again not surprising, the frequency of chromosomal abnormalities was far smaller in induced than in spontaneous abortions, perhaps one-fifth to one-eighth as much (Carr 1965, Sasaki et al. 1967, Yamamoto et al. 1976), but understandably about five or more times than that found in newborn generally.

An extensive search of the medical literature of the time found that 0.62% of karyotyped infants had major chromosomal abnormalities and that about 6% of serious malformations in live born children were associated with such abnormalities (Kalter and Warkany 1983), a finding substantially corroborated 20 years later (Rösch and Steinbicker 2002)

But it was in neonates and older infants that the teratologic consequences of chromosomal aberrations, especially autosomal trisomies, soon became best demonstrated; and their largely nonspecific outcomes revealed. Thus congenital cardiovascular malformations of various sorts were discovered to occur in all of them, trisomy 13–15, 18, and 21 (Warkany et al. 1966, Polani 1968).

Turning the table, a number of studies were made of chromosome abnormalities in fetuses with heart defects, many of which were found to possess a substantial frequency of them. In a Yale study in 1985–6 of pregnancies referred for "generally recognized risk factors," trisomies were found in one-third of the 7% of fetuses with heart defects (Copel et al. 1988); and in a larger number of fetuses examined in 1984–91 in Yale 23% of those analyzed had trisomic abnormalities, 43% Down syndrome and a similar number trisomy 18 (Smythe et al. 1992). The particular heart defects in these cases were not specified, although the seriousness of those

in Down syndrome may be deduced from the fact three-quarters of them were terminated or died in utero. No doubt many of the atrioventricular septal defects comprising 22% of the heart defects were present in these cases.

Details about the frequency and type of chromosomal abnormalities in fetuses at high risk for heart defects were provided by a 1987–93 study in Berlin (Chaoui et al. 1999). Chromosome abnormality was present in 23% of those with heart defects, with highly specific association. Ventricular septal defect occurred in about half of the trisomy 18 and atrioventricular septal defect in about 70% of Down syndrome, i.e. with little overlap between the conditions in one and the other. Further, the association of heart defects and chromosomal abnormalities is far more frequent prenatally than in the neonatal period, no doubt because of prenatal death of chromosomal abnormals.

In a study made at King's College Hospital in London chromosomal abnormalities were diagnosed by chorionic villus sampling in fetuses identified by increased nuchal translucency thickness as being at risk of heart defects (Hyett et al. 1997). The pregnancies were terminated early and at examination heart defects found that were quite specific to the trisomic anomaly. Both atrioventricular and ventricular septal defects occurred in Down syndrome, but as usual with a greater frequency of the former than the latter. In the other trisomic states the atrioventricular septal defect seldom or never occurred, but on the contrary contained predominantly or only ventricular septal defects. Another aberration, found in fetuses in all groups, narrowed aortic isthmus, was much increased in fetuses with high degrees of nuchal thickness, and thought to be the basis of the thickness.

A study made in 1994–7 in Naples dealt with heart defects in Down syndrome (Paladini et al. 2000). In fetuses from referred pregnancies who were known to have the syndrome, about a quarter each had atrioventricular or ventricular septal defect and a few others various other heart defects. A minute number had extracardiac defects. The study also reported on the scanning of fetuses from pregnancies with specific risk factors, of which however only 8% had heart defects, and of them 5% Down syndrome. Atrioventricular septal defect was found in 9% of those with heart defects, about half isolated and half in Down syndrome. Ventricular septal defect, though occurring in 17% of those with heart defects, was seen in none of the Down syndrome. That is, in the heart defect group 43% of those with atrioventricular septal defects had Down syndrome, whereas none of those with ventricular septal defects had Down sydrome, evidence of much specificity.

A word can be added about early death of heart deformed infants. Where such facts were recorded it was noted that the majority of deaths of children with heart defects occurred very early in life. For example, in 1941–60 in Sweden almost 31% of heart defect cases died in infancy, 46% in the 1st week and 72% in the 1st month (Carlgren 1959). In a London hospital in 1970–3 38% died in the 1st week, 55% by 1 month, and 64% by 1 year (Miller 1974). There was some improvement in the rate, even during the brief period surveyed; thus in 1970 64% were alive at 1 month, 83% in 1973, etc. In a Swedish survey in 1961–70, 31% were dead by 1 week, 50% by 1 month, etc. (Esscher et al. 1975); and in Toronto of data from 1950–70, 34%

were dead in the 1st month, 71% the 1st year (Keith 1978). In a hospital in Norway in 1982–96 half died neonatally and almost three quarters before 1 year of age (Meberg et al. 2000). In California approximately two-thirds of deaths attributed to congenital heart disease in 1957–60 occurred in infants, the great majority in the 1st week (Allen 1968). Later in California, in 1960–6, mortality was highest on the day of birth, 9% dying during the 1st week. A US nationwide survey in 1979–88 noted a heart defect mortality rate of 0.71/1000 live births in the 1st year of life, 59% in the 1st month (Gillum 1994). A 1985–90 survey in northern England noted 70% dead within the 1st month of life (Abu-Harb et al. 1994).

CHAPTER 13

# PRENATAL DETECTION

## INTRODUCTION

With the arrival of the 1990s the study of gross anatomical features of cardiovascular malformations in spontaneous abortions using conventional procedures came largely to an end. Instead, other procedures became dominant in prenatal studies of cardiac maldevelopment, procedures whose initial and primary purpose was readying for obstetric management and postnatal care, and secondarily for facilitating termination of affected pregnancies. Thus while the emphasis of the abortion studies had been epidemiologic, that of the newer prenatal ones was pragmatic.

The new methodologies and their practical purposes were soon widely adopted. For the most part, especially in the earliest years, the goal of such studies was far from, indeed could not have been, learning the full and accurate frequency of cardiovascular defect in embryos and fetuses. This hardly needs stating, since most if not all the pregnanies surveyed were those that were referred because of various indications of elevated risk, and thus were obviously a highly unrepresentative group.

Despite a main interest of this section of the present work being the frequency of cardiovascular defect in embryos and fetuses, as the complement to those detected postnatally, a full exploration of the topic requires that some review and discussion of these new studies, those of fetal scanning, be included.

An early use of an advanced form of ultrasonographic visualization of fetal congenital malformation set the pattern for those that followed. Women seen in the obstetrics department in King's College Hospital in London in 1978–82 were those who were referred because of having prior affected children and other real and supposed risk indications (Campbell and Pearce 1983). Though the heart could be visualized at about 16 weeks of gestation, making the examination some weeks later enabled a more detailed one, and allowed many more types of structural anomalies to be detected. The defects found were briefly described, including two associated with chromosomal anomalies, a Down and a Turner syndrome, the frequency noted being 30.6/1000 fetuses scanned.

Numerous studies of this kind soon followed. At Yale University in New Haven in 1984–5 pregnant women were referred for some of the usual fetal risk indicators

(Copel and Kleinman 1986). Examination mostly at gestation weeks 19–22 found a frequency of defects of 63.6/1000; but in those with a family history, constituting almost half of the referrals, the frequency was only 8.9/1000; in the next largest reason for referral, maternal diabetes mellitus, no defect was found in the fetuses. The most common defect, present in half of the fetuses, was complete atrioventricular septal defect, only one of which in Down syndrome. Over one-third of the affected fetuses also had a wide variety of associated noncardiac defects. Last, only half of the suspicions of an anomaly on a general scan were positive. This degree of success was also had in a study in Rotterdam scanning pregnancies of women referred for various risk indicators, finding a frequency of 56.5/1000, over one-third with abnormal chromosomes (Wladimiroff et al. 1985).

Many referred women were echocardiographed in Guy's Hospital in London to test the accuracy of the procedure (Allan et al. 1984). Perhaps because this was done over a wide gestation period, beginning at 13 weeks, a diversity of defects was identified, with a frequency of 21.2/1000, none predominating however. One of the more common ones was atrioventricular septal defect, none apparently in Down syndrome. More than half were associated with noncardiac malformations. A small number with isolated cardiovascular malformations died in utero, almost all the others diagnosed were confirmed by necropsy, all in all validating the diagnoses.

Once more the composition of the pregnant women made it obvious that the outcome was hardly likely to be typical of the overall population. The first subjects, one-quarter of all, included for "practice" in the use of echocardiography, had normal pregnancies, and, remarkably, as it turned out, none had fetuses with abnormal hearts. The others, referred as usual because of various factors indicating increased risk of congenital heart disease, thus clearly bearing no resemblance to representativeness, had a frequency of 28.3/1000. Also indicating that the findings were no guide to the general problem was the high mortality rate of the offspring, due to the severity of most of the defects and their frequent association with serious noncardiac abnormalities.

Not only were referred cases unrepresentative of the overall population, they were unrepresentative as well of all cases at risk, since few women whose children had mild defects were referred (Allan et al. 1985). This further added to the difference between the spectrum of defects seen at scanning and that after delivery; the former being more severe and often associated with other more lethal defects.

In a continuation of the project the search was widened to include women referred to Guy's Hospital from the south of England and Wales in 1985–7, sometimes as late as 28 weeks of pregnancy (Davis et al. 1990). The majority were referred because of an abnormal four-chamber view seen at a routine scan in the referring hospitals. Incidentally, the number identified through this initial diagnostic step grew exponentially from 1982 to 1990 (Cullen et al. 1992). Structural cardiac abnormalities were diagnosed in 67.0/1000 fetuses, the most frequent in order of frequency being atrioventricular septal defect, coarctation of the aorta, ventricular septal defect, and hypoplastic left heart, totaling almost half of all. The rather remarkable frequency of the first and most common of these, atrioventricular septal

defect, 11.4/1000, was not described as occurring in Down syndrome, in which it is very often found, despite over half of the karyotyped fetuses having a chromosomal aberration. The great seriousness of the defects was reflected in the poor perinatal and neonatal outcomes, 36% terminated and 39% stillbirth and neonatal death. Diagnosis failed in another 8.3/1000 defective fetuses, almost half of them with major abnormalities.

The frequent occurrence of heart defect in chromosomal abnormality, as noted above, prompted an analysis of the phenomenon (Allan et al. 1991a). The defect in cases seen in Guy's Hospital in a preceding 10 year period consisted most commonly of atrioventricular septal defect in trisomy 21, variations of tetralogy of Fallot in trisomy 18, coarctation in Turner syndrome, etc. A major proportion were diagnosed after 28 weeks of pregnancy, i.e. in stillbirths, and thus of no help in estimating frequency in fetuses. In cases diagnosed in the latter part of this period, which were apparently recorded in greater detail, the frequency of chromosomal abnormalities was 57%; but when based as well on gross malformations attributable to chromosomal abnormalities it was estimated that 16–17% of conceptuses with heart defect had chromosome anomalies. Again the proportion of cases that were fetuses and stillbirths was not noted.

The number of high-risk referrals seen at the Guy's Hospital fetal cardiac center grew arithmetically in 1980–92, and the number of fetuses with cardiac anomalies detected grew correspondingly (Allan et al. 1994). Heart malformation was diagnosed in 10% of pregnancies, two-thirds at less than 24 weeks of gestation, with the week of detection decreasing annually. What remained unanswered was the frequency of cardiovascular malformations at conception, so to speak, and at the time of birth as reduced by those eliminated during the course of pregnancy.

From the perspective of the present work, a most significant, and quite incidental, part of this report, was its comparison of the frequency of particular malformations in fetuses and in infants. Among the commonest detected in the former, atrioventricular septal defect and hypoplastic left heart syndrome, were among the least common in the latter; and least common in the former, ventricular septal defect, complete transposition, tetralogy of Fallot, Ebstein's malformation, were the commonest in the latter. The same contrast was reported elsewhere (Allan et al. 1985, Friedman et al. 1993, Montana et al. 1996). This discrepancy was given a simple, and nondevelopmental, explanation: the former abnormalities being more readily detected prenatally than the latter, enabled "most parents to choose to terminate the pregnancy after the prognosis . . ." (Allan et al. 1991b).

Allan continued these studies after he moved to the Presbyterian Hospital in New York (Brick and Allan 2002). In cases referred in 1993–9 for fetal cardiography the overall rate of congenital heart malformations diagnosed at 15–42 weeks of pregnancy, almost half before 24 weeks, was 16%. This steadily increased, which was not adequately explained, reaching 25% in later years. Half of the conditions diagnosed were atrioventricular septal defect, hypoplastic left heart syndrome, tetralogy of fallot, and ventricular septal defect; 15% included extracardiac defects, over half with chromosomal abnormalities.

In the Fetal Cardiovascular Center at the Yale School of Medicine in New Haven, Connecticut in 1984–91 patients with the usual assortment of known and alleged risk factors were referred for fetal echocardiogram (Smythe et al. 1992). Cardiac malformations were diagnosed in 5.7%, with atrioventricular septal defect at 22% and aortic valve atresia at 13% predominating. One third had major extracardiac malformations, 29% of these with chromosomal abnormalities, while in all 13% had such anomalies. Again, while family history was the commonest risk factor, at 30%, only 2% were positive.

The likelihood of cardiac defects being detected prenatally largely depends on their severity and complexity, especially when associated with noncardiac ones. This was again demonstrated by a study that claimed to use a population based approach, but as conventionally defined did not do so, to examine the trend in surveillance of cardiac defects (Montana et al. 1996). The frequency of cardiovascular malformations in the 1st year of life in all infants born in the Atlanta area in 1990–4 was 8.2/1000.

While this is undisputed, the proportion diagnosed prenatally is unclear, because prenatal diagnoses of heart malformations were made in cases discovered retrospectively to have been referred for fetal echocardiography, but whose total number was not noted. The findings are therefore irrelevant so far as population incidence is concerned, but yield general information. Thus for whatever it is worth, the overall proportion of defects diagnosed prenatally was 6%, which continually increased from 3% in 1990 to 13% in 1994. At the same time the gestational time of detection decreased from 29 to 25 weeks, explained by the rise in the proportion of affected infants referred for prenatal diagnosis. Not unexpectedly, the proportion of specific defects detected prenatally varied markedly, ranging from about 5% for ventricular septal defect to 28% for hypoplastic left heart syndrome; and being multiply malformed increased mortality, both prenatal and postnatal. In addition, the spectrum of defects diagnosed prenatally differed strikingly from that diagnosed postnatally; e.g., 13% of atrioventricular septal defects were found prenatally compared with less than 5% in all.

In one of the latest studies of this sort, in the Helsinki Children's Hospital in 1983–95, women with the usual assortment of risk indications were referred by obstetricians at 16–41 weeks of pregnancy for detailed echocardiographic study by a pediatric cardiologist (Eronen 1997). It is notable once more that while a third of the referrals were because of family history, especially a previous affected child, only 2% had a structural heart defect. Also of interest, no fetus of diabetic women had a heart defect. In all, 13% had structural abnormalities, three-quarters dying in utero or postnatally. Almost 40% were associated with chromosomal abnormalities, particularly ventricular septal defect and atrioventricular septal defect, together composing over three-quarters of the defects with these abnormalities.

A small number of high risk pregnancies were studied in 2001–2 at a hospital in Toronto (McAuliffe et al. 2005). Echocardiographic screening at 12–15 weeks of gestation detected cardiac defects (omitting the two instances of ectopia cordis)

in 12% of cases examined. The point was made that such early diagnosis detects a large proportion of cardiac defects.

A study in 1995–9 in localities in northern Israel also looked into the potential of early fetal scanning (Weiner et al. 2002). Women with features indicating high risk for cardiovascular malformation, especially maternal diabetes and prior affected pregnancies, were first echocardiographed at 11–14 weeks, in most instances transvaginally, and when necessary at later times, transabdominally. In fewer than 3% of the earliest examinations, and even fewer of the later ones, were malformations detected, if I have interpreted the tabular material correctly. In fact it is not easy to interpret most of this article, since the number of women examined at the various times and other details were not clearly denoted.

## POPULATION SCREENING

It was gradually realized (why it should have taken time at all to do so is perplexing) that examining fetuses of referred patients is unsuitable for discovering the prenatal rate and spectrum of cardiovascular malformations in the overall population. As is true of congenital malformations generally, the great majority of defects of the cardiovascular system occur in the absence of known risk indicators. It bears remembering that even the feature most indicative of heart problems, family history, gives as little as a 2–3% recurrence rate (e.g. Allan et al. 1994, Eronen 1997). Hence it appears that only by prenatally screening all the pregnancies in a population can the true frequency of cardiovascular malformations hope to be established. This assumes of course that no malformed heart will escape detection for whatever reason. But in time it became obvious that this assumption too is unrealistic (Sharland 1997). Accomplishing, but still not guaranteeing, the goal of total surveillance thus required the whole-population approach.

This approach in fact was essential for many purposes, e.g. for judging the effectiveness of different scanning procedures in detecting fetal cardiovascular malformations. But this too had limitations. In one British locality in 1989–91, though almost all women were examined in local hospitals by midtrimester fetal ultrasound, in only a small minority was a cardiac defect suspected (Cullen et al. 1992). So far as this small number was concerned, almost all upon further referral to a regional center in London were found to have cardiovascular malformations, 29% of a nonsevere and the remainder a severe type, the great majority tetralogy of Fallot and atrioventricular septal defect; of the latter 4.5% had associated noncardiac defects, and of all only 2.5% had a family history. The total number of women examined was not noted, hence the success rate is unknown.

A variant study was made in the South East Thames Region in the early 1990s (Sharland and Allan 1992). Again all pregnant women were routinely examined; but in this case done in selected obstetric units whose personnel had been trained to recognize cardiovascular malformations through four-chamber view scanning. Women with suspected abnormalities were referred to a center in London, their number increasing yearly, especially since introduction of the four-chamber method.

The defects were mostly hypoplastic left heart and atrioventricular septal defect, but the total number scanned was not noted.

The bizarre thinking of scanning practitioners was shown by the conclusion that, "the perinatal mortality in a screened group was significantly lower than in a control group, the difference being due to the detection of major fetal anomalies by ultrasound screening and subsequenct termination of pregnancy." This presumably is what prevention of malformations was thought to consist of. At the same time, termination was feared by some professionals, since it "raised concerns about the future practice of paediatric cardiology"; but this dire fear was averted since the rate of interruption did not seem to be increasing (Sharland 1997).

The population approach was also used in the Lombardy region of Italy in 1985–8, to compare ultrasonography with and without the four-chamber view (Vergani et al. 1992). The overall frequency of cardiovascular malformations at delivery, pregnancy termination, and autopsy was 5.2/1000. Surveying all pregnancies allowed the comparison, and showed that the more efficient procedure was about twice as effective, 81% vs 47%; which was just on the borderline of statistical significance. Whether the difference was entirely due to the use of the procedure and not perhaps in part to fuller experience was apparently not considered.

A similar study was made in the Trondheim region of Norway (Tegnander et al. 1995). In a prospective study in 1986–91 almost all pregnant women were scanned for the purpose of comparing the efficacy of general anatomical survey of the fetus and four-chamber view of the heart in detecting critical and noncritical defects. At birth the frequency of "critical" cardiovascular malformations was 3.4/1000, and that of "noncritical" 8.7/1000. No noncritical, i.e. mild, defects were diagnosed prenatally by either procedure; and although the four-chamber view detected a larger proportion of critical defects, 39%, than did the survey, 18%, the difference was not statistically significant, no doubt because of the small sample sizes. The somewhat greater success was probably due to the larger rate of associated disorders.

In a modification of the population approach, practiced in a medical center in Tel Aviv, scanning of low-risk pregnancies at 18–24 weeks of pregnancy with the standard four-chamber view was compared with extended echocardiography (Achiron et al. 1992). The frequency of major structural cardiac defects in births was 3.9/1000, of which 86% had been diagnosed prenatally. Extended examination appeared to be the more sensitive, but small numbers made this uncertain.

A further Tel Aviv study of low-risk pregnancies in 1991–3 used transvaginal rather than transabdominal echocardiography and at an earlier than usual fetal stage, 13–15 weeks of gestation (Achiron et al. 1994). The frequency of diagnosed major structural cardiac malformations at birth was 4.5/1000, all detected prenatally, consisting of one each of patent trucus arteriosus, tetralogy of Fallot, and aortic atresia. The procedure the authors felt reliably diagnosed defects recognizable at this early stage, and enabled early parental decision about pregnancy interruption.

In the Northern Region of England almost all pregnancies in 1990–2 were prospectively scanned by four-chamber view (Wyllie et al. 1994). Of the 6.5/1000 heart malformations in infants 23% were diagnosed prenatally, a little over half

complex or significant and the remainder mild. The prenatally detected defects must therefore have consisted of some of the more serious ones, while the less serious ones remained undetected or undetectable in the hands of the radiographers and technicians.

It thus seems that the stage then reached in the evolution of scanning equipment and in the competence of radiographers left many types of cardiovascular malformations undetected prenatally, whether severe or nonsevere, associated with chromosomal and other abnormalities or not, and hence unable, if it were feasible at all, to establish the prenatal prevalence of cardiovascular malformations. That the experience of the investigator was a paramount determinant of the quality of prenatal ultrasound was supported by a study comparing the detection rates in different types of medical facilties (Bernaschek et al. 1996).

Women attending a prenatal-care unit in 1993–4 in Vienna were screened by detailed echocardiography at 18–28 weeks of gestation (Stümpflen et al. 1996). Many had a variety of risk factors, but in those with none, cardiovascular malformations were detected in 6.9/1000 fetuses scanned. The strength of risk factors was shown by the frequency in the group with them being 34.3/1000. This amount was of little surprise, but even the amount in the other group was made suspect by the possibility that none of the women may have truly been representative, since they attended a clinic in a Department of Prenatal Diagnosis and Therapy, with no statement of how they came to do so.

Women from the Rotterdam area without known risk indicators scheduled in 1991–3 for routine examination were four-chamber sonographed at 16–24 weeks of gestation in ultrasound centers (Buskens et al. 1996). Offspring followed for 6 months after birth had a frequency of 8.3/1000 cardiovascular malformations, only 4.5% of which were detected prenatally. The authors were forced to admit that routine 2nd-trimester fetal four-chamber view "does not provide an accurate screening test . . . and that even major anomalies . . . were not detected prenatally to a satisfactory degree." A number of factors was named in attempting to explain this poor record; but none it seemed gave promise of future improvement.

Women were consecutively scanned in a Michigan hospital at 14 weeks or more of gestation in 1990–5, usually, but apparently not always, for routine evaluation of fetal age and growth (Kirk et al. 1997). At birth or autopsy cardiovascular malformations were diagnosed in 6.9/1000 infants, two-thirds, 4.5/1000, detected prenatally. However 8% of the women were referred because of a suspected fetal cardiac anomaly, and 10.1/1000 of their offspring had a cardiac abnormality at birth, in contrast to 6.6/1000 in the remainder. How many of the former were detected prenatally was not explicitly noted. While 21% of the entire number had an associated noncardiac defect, the number of the fetuses from unselected and selected women with associated noncardiac defects was not stated separately. The rate of detection, again not surprisingly, varied greatly depending on the severity of the defect.

In a study in Vienna, of births of unselected women delivering in 1992–6 the frequency of cardiac malformations in newborns was a low 1.3/1000, 25%

associated with chromosomal or other malformations, with a prenatal diagnosis of 45%, all detected at week 22 or earlier (Hafner et al. 1998).

A UK collaborative effort had as its principal purpose determining the effect of fetal cardiac screening on the prevalence of cardiovascular malformations (Bull 1999). Data from 1994, a year of full ascertainment, revealed that about half of the fetuses diagnosed with cardiovascular malformations were terminated. This was especially so for the commonest ones, hypoplastic left heart, atrioventricular septal defect, and univentricular heart, the termination rate varying from 66% for hypoplastic left heart to 11% for tetralogy of Fallot. It was estimated that nationally there were 2.12 affected pregnancies per 1000 livebirths and 1.74 affected livebirths per 1000 livebirths. From this information it was calculated that fetal diagnosis and intervention had trivially reduced the number of affected births.

A retrospective study in 1996–9 at a hospital in Bari, Italy similarly examined the potential impact of prenatal diagnosis of congenital cardiovascular malformations (Vimercati et al. 2000). Newborns and terminated pregnancies, in two time periods, were compared with fetuses ultrasonically screened at 18–22 weeks of gestation. The frequency at birth was 4.6/1000 in the earlier period and 5.4/1000 in the later, and in aborted fetuses 10% and 11% respectively, neither difference being statistically significant. Nor did the prenatal detection rate improve, being 25% and 27% in the two intervals. It seemed therefore that with certain exceptions advance in experience with fetal echocardiography had made little difference.

A retrospective review of all pregnancies in the Isère district of France in 1989–95 found a frequency of cardiac abnormalities in scanned fetuses and infants up to the age of 1 year of 3.2/1000, 35% detected prenatally (Klein et al. 1999). Several comparisons of the sensitivity of prenatal detection were made: cardiopathies of high vs low risk, the former detected earlier in pregnancy than the latter, with detection rates of 54% and 27% respectively; isolated (58% of all) vs associated malformations, 26% and 48% detected respectively. The detection rate of high risk defects was not increased by the presence of additional malformations, but that of low risk ones was increased. Finally the overall frequency in 1989–93 was compared with that in 1993–5, with the difference not statistically significant.

Unselected women prospectively seen in a large number of European obstetric units in 1990–3 were screened to detect congenital malformations in fetuses, abortuses, and neonates (Grandjean et al. 1999). The detection rate of major and minor cardiovascular malformations, presumably of all such defects, was 39% and 21% respectively, far less than for central nervous system and urinary tract malformations.

Another prenatal indicator of cardiovascular malformation, excessive nuchal translucency thickness (subcutaneous edema in the fetal neck region), was analyzed in a retrospective study of women delivered before mid-1997 at Guy's Hospital in London (Hyett et al. 1999). Major cardiac defects were found with a frequency of 1.7/1000 pregnancies, two-thirds diagnosed in fetuses, the remainder in newborns. The frequency increased with nuchal thickness, 55% associated with a thickness greater than the 95th percentile as measured at 10–14 weeks of gestation. The variety

of defects was not unusual, except that the defect most closely associated with thickness was coarctation. Atrioventricular septal defect was only found in fetuses diagnosed by ultrasonography at 16–32 weeks of pregnancy; overall its frequency was 0.10/1000 pregnancies, and constituted 6% of all the defects found. This method of detecting cardiac defects prenatally compared favorably with the four-chamber method. The low overall frequency may have been partly due to only presumably chromosomally normal fetuses being screened.

Further evidence of the efficacy and validity of prenatal diagnosis of heart defects by increased nuchal thickness was gathered in a study at King's College Hospital in London, whose primary purpose was to gauge the feasibility of using this as a means of diagnosis in early fetal life (Huggon et al. 2002).

A similar study in Vienna in 1994–2000 focused on the relation between cardiovascular malformations and nuchal translucency in euploid fetuses (Hafner et al. 2003). The frequency of major cardiac malformations was 1.9/1000 (omitting 2 ectopia cordis), 89% detected prenatally, 81% isolated. Only the 20% of fetuses with associated defects had an excessive nuchal translucency thickness. The women entering the study were 1st-trimester volunteers; how this may have prejudiced the outcome was not discussed.

Another European multicenter study in 1996–8 using hospital- and population-based data was made of congenital heart malformations routinely diagnosed prenatally by ultrasonography or within the 1st week of life; with the emphasis in one report on isolated defects (Garne et al. 2001) and in a second report on cardiovascular malformations associated with major noncardiac defects of chromosomal or other origin (Stoll et al. 2001). The rate of prenatal diagnosis of all cardiovascular malformations (i.e. isolated plus associated) was 25%; for isolated defects alone, which comprised about two-thirds of them all, it was 16%, while nearly half of the associated defects were detected prenatally. These however are mean rates, and were perhaps misleading, since they varied considerably from region to region. As did the success of prenatal diagnosis of individual defects, which, not surprisingly, varied by severity of condition. As to the absolute frequencies, that of all defects was 3.4/1000 births, 2.4/1000 for isolated defects, and 1.1/100 for associated ones.

In as near a conclusion as was come to, in the first of these reports the debatable statement was made that "... good ultrasound equipment and training of staff increase the prenatal detection rate ..." Quality of training and equipment may explain between-region differences–and give hope that when all regions have attained the high standard of western European all will have as good a detection rate as was found there. But for these data the passage of the years provided little evidence that even in the latter areas the detection rate was substantially better than it had been previously.

In the Troms and Finnmark regions of northern Norway in 2001–2 more than 95% of all pregnant women received routine ultrasound screening at 18–20 weeks of gestation, and those with abnormal or suspicious signs were referred for further fetal heart assessment (Acharya et al. 2004). In this period the total frequency

of major cardiovascular malformations detected was 4.4/1000, of which 24%, i.e. 1.1/1000, were identified prenatally.

The effects of the increasing rate of prenatal diagnosis and pregnancy termination on the perinatal frequency of cardiovascular malformations and mortality were examined in a Paris study (Khoshnood et al. 2005). The analysis had in its favor that it covered a 20-year period of prenatal diagnosis, 1983–2000, and that it was population based. The frequency of cardiovascular malformations, collected by various hospital services, and diagnosed by pediatric cardiology examination or autopsy, was 5.39/1000 births plus terminations, or 4.38/1000 upon exclusion of the 18% associated with chromosomal abnormalities. The increased number of cases over time was probably due, among other things, to the detection of less severe conditions, especially of ventricular septal defect, whose overall frequency was 1.38/1000 births and terminations. Most recently over half of all cases of isolated cardiovascular malformations were detected prenatally, and a large proportion of affected pregnancies terminated, in particular those of the most severe defects. Thus this study appeared to record progress.

## SCREENING OF ALL CONGENITAL MALFORMATIONS

Routine prenatal diagnosis of all congenital maformations, including those of the heart, has become prevalent in recent years. Earlier reports of such studies were often missing various details, hence are omitted here; for interested readers some were cited in Shirley et al. (1992). Some later ones are noted here. One reason for including them is to compare the prenatal detectability of cardiovascular malformations with that of other malformation types, especially of neural tube defects, one of the most detectable of all it seems.

Studies of this inclusive sort were made early in part of the province of Hainaut in Belgium, the groundwork laid by a preliminary survey in 1979–82 (Borlée-Grimee et al. 1984). The survey found that the frequency of cardiovascular malformations was 9.7/1000 in all births and 40.2/1000 in stillbirths, the latter comprising 40% of such defects in all births and almost one-quarter in stillbirths. This may have been a faulty estimate since some minor or questionable defects were included in the total count. The total frequency of neural tube defects was 1.7/1000 births, about one-sixth as frequent as those of the heart. (As will be seen in the second volume of this work, the frequency of neural tube defects varies significantly geographically.)

A study in the same region in 1986 focused on the proportion of malformations in all births up to the age of 1 year detected prenatally (Lys et al. 1989). The frequency of cardiovascular malformations was 8.6/1000 and of neural tube defects 1.3/1000, approximating the earlier findings. Setting the pattern for future such studies, prenatal diagnosis, which was made at various times during pregnancy, detected 2.8% of cardiovascular malformations 50% of neural tube defects, the former not diagnosed till quite late in pregnancy. In sum, therefore, while cardiovascular malformations were over six times more frequent at birth than neural tube defects, the latter were over 20 times more often detected prenatally.

A still later Belgian study seemed more efficient. Several ultrasound laboratories cooperatively conducted a prospective study in 1984–9 to compare the congenital anomaly findings in scanned fetuses with those in neonates (Levi et al. 1991). Excluding selected high-risk pregnancies, the frequency of cardiovascular malformations, at 6.1/1000, was the commonest of all defects, five times more so than those of the neural tube, 1.2/1000, but once more were detected prenatally far less frequently, 24% vs 65%. The authors noted the consensus opinion that, for various reasons, "not all anomalies are detectable before 23 weeks." This was especially true of the cardiovascular malformations, since in this survey while 2.9% of cardiovascular malformations were detected at or before week 22, almost 20 times as many neural tube defects were detected that early. It may seem a tautology, but part of the reason for the greater detectability of the latter is that they are far more noticeable. Almost one-third of the undetected anomalies overall were termed mild and one suspects that a substantial proportion of these were cardiovascular malformations.

In southern Finland in 1980–8 almost the entire pregnant population of the area was routinely ultrasound screened, at 18 weeks of gestation only or also at 34 weeks (Rosendahl and Kivinen 1989). The newborn were examined and records of infants checked from 2 months to 2 years. Despite this lengthened observation period a relatively low frequency of congenital malformations of 1.03% was discovered, of which 58% were detected prenatally. This however was approximately the frequency reported to a Finnish register of congenital malformations in 1963–81 (Saxén 1983). Lists of various classes of malformations were presented, among them neural tube and heart defects. The frequency of the former was 0.67/1000 births, rather smaller than the 0.95/1000 births found in southern Finland by a congenital malformation register in 1970–83 (Lindy and Autio 1985). Finland is acknowledged to have a low rate of these defects compared with most European countries. Of the defects 83% were diagnosed prenatally. The frequency of cardiovascular malformations, however, omitting the two occurrences of ectopia cordis, was a more usual 2.2/1000, comprising a large variety of anomalies, including one atrioventricular septal defect, about a third of them diagnosed prenatally. These findings, coming from a large number of unselected pregnancies, must be trusted truly to represent the rate of occurrence of these malformations in this population.

A large number of low risk pregnancies was examined by ultrasonography in 1988–9 at a hospital in Luton, Bedfordshire (Chitty et al. 1991). All women who booked early enough were examined in the 2nd trimester by radiographers with various amounts of experience in this task. A wide variety of structural congenital malformations were detected, with a total frequency of 15.0/1000, lethal or severe ones constituting 70% of the total. Three-quarters of the malformations were diagnosed prenatally, and 42% terminated. Of the total, 8.9% were cardiovascular and 16.8% central nervous malformations, 64% of the former and 95% of the latter prenatally diagnosed, 1.3 and 2.5/1000 pregnancies respectively.

Three studies made at about the same time and in areas near each other in southeast England presented some apparent contradictions. In one, a routine

prospective evaluation at a hospital in Berkshire was made in 1988–91 of the effectiveness at 19 weeks of gestation of fetal ultrasound detection of structural abnormality (Luck 1992). Comparing frequency at birth, defects of the heart, as usual, were more frequent than those of the neural tube, 3.2/1000 vs 1.3/1000, but their rate of prenatal detection on the contrary, as usual, was the opposite, 41% vs 100%; of all malformations scanned for, those of the heart were the most difficult to detect.

In the second study, in 1989–90 in Middlesex, all pregnant women were routinely ultrasound screened at 19 weeks of gestation (Shirley et al. 1992). Again there was a difference between the frequency at birth of heart and neural tube defects, but the reverse of the more usual one, the former being less common than the latter, 1.4/1000 vs 2.2/1000; with as usual fewer detected prenatally, 56 vs 100%. It may be further mentioned that while all cardiovascular malformations were terminated only 85% of the latter were so eliminated. The impact of this elimination on frequency at birth was not commented on.

The two studies just mentioned may be compared with another in the same region of southeast England made a few years later. All women in Oxford, England were prenatally scanned at 18–22 weeks of pregnancy in 1991–6 (Boyd et al. 1998). Again as usual, cardiovascular malformations were more prevalent than neural tube defects, 2.7/1000 vs 1.4/1000 births. But, again as usual, the former were far less often prenatally detected than the latter, 38 vs 96%. This may have been an underestimate, since some perhaps significant number of malformations were not those ordinarily considered major. The rate of prenatal detection increased with time, presumably owing in part to improved technology and more experienced technicians.

Here then are three studies in southeast England done during about the same period, one of which was different from the others. This difference–neural tube defects being more prevalent and cardiovascular malformations less in Middlesex than in the other two–is difficult to explain. As a matter of fact the neural tube defect prevalence in Middlesex was far closer to the one found in an extensive study in southeast England in 1965–8 than in the other two areas (Carter and Evans 1973). But on the contrary, that of cardiovascular malformations was smaller, which leads one to suspect that that is where the trouble lies.

As mentioned above, one purpose of prenatal diagnosis was to manage pregnancy outcome by aborting affected fetuses. It was only natural then to ascertain the impact this practice had on the frequency of heart malformations at birth. This matter was pursued by several studies, one an examination of births surveyed by a registry in the Marseille area in 1984–90 (Julian-Reynier et al. 1994). The upshot was that the prevalence of heart abnormalities at birth was but barely affected by prenatal diagnosis of cardiovascular malformations. The frequency of isolated heart defects at birth was 5.3/1000, of which a mere 0.8% were eliminated by prenatally diagnosis and termination (time of prenatal diagnosis not noted). This in contrast to neural tube defects, at 1/1000 one fifth the frequency of cardiovascular malformations, but 32% of which were terminated.

A rather higher rate of elimination of cardiovascular malformations was achieved in a study in the Mainz area (Queisser-Luft et al. 1998). Its goal, another use prenatal screening of unselected pregnancies was put to, was identifying risk factors by comparing affected and unaffected offspring. It focused on four major malformation categories in all births in 1990–4. The neonatal frequency of two of this selection of malformations, heart and neural tube defects, was 3.3/1000 and 1.2/1000 respectively, of which 6% of the former were detected prenatally and half terminated; and 68% of the latter detected prenatally and over half terminated. Neural tube defects were detected at a wide range of times of scanning, whereas successful detection of cardiovascular malformations was confined to fairly late weeks. Efficacy of prenatal diagnosis of neural tube defects seemed to increase with time, but that for the heart seemed stagnant. The case-control means of searching for risk factors appeared to implicate a wide assortment of factors, such as consanguinity and maternal alcohol abuse, and to challenge the idea that the majority of malformations occur in pregnancies without specific risks. It does not seem however that the findings would have been of much predictive helpfulness.

The effect of terminating pregnancies with malformed fetuses on malformation frequency was also examined in two other studies, in Boston and in Western Australia. The Boston study, conducted at the Brigham and Women's Hospital, focused on malformation rates as affected by trends in elective pregnancy termination (Peller et al. 2004). During the years selected to be surveyed, from 1977 to 1999, terminations increased, but only in the later years surveyed, and concomitantly stillbirths and neonatal deaths steadily declined. At the same time, although ultrasonography use greatly increased, the rate of severe malformations in neonates was not significantly changed, and stubbornly the overall frequency of major malformations remained consistent at about 2%. Data for heart defects per se were not listed; a possible clue was Down syndrome, terminations for which rose somewhat over the period. A synthesis of these bits of information was studiously avoided.

The study in Australia was concerned in part with the impact on perinatal mortality (Bourke et al. 2005). The frequency of congenital cardiovascular and nervous system defects up to 1 year of age in births in 1980–98 was 7.6/1000 and 1.8/1000 respectively, of which 0.8 and 33% were terminated, generally duplicating the pattern seen elsewhere.

All pregnant women in the Swiss Canton of Vaud were screened to determine the sensitivity of improved ultrasonography in diagnosing malformations (Vial et al. 2001). The practice in this area, as it was in some others, was to conduct an initial scan at 11–14 of gestation and a second and third later. The frequency in births in 1994–8 of cardiovascular malformations was 3.6/1000; 23% of them were diagnosed prenatally, varying from 36% for major ones to 18% for others. In contrast once more were neural tube defects with a frequency at birth of 1/1000, but of which 87% were diagnosed prenatally. Thus while ultrasound screening may have improved since the 1980s, as the authors claimed, prenatal detection of cardiovascular malformations seems to have partaken but little in this supposed improvement.

Retrospective study of all births in maternity hospitals in the Strasbourg region of France in 1979–99 found an overall congenital malformation frequency in newborns of 3.2%, and for isolated and associated cardiovascular malformations and neural tube defects rates of 9.6/1000 and 1.0/1000 respectively (Stoll et al. 2002). (The former large rate obviously stemmed from including ventricular septal defects, accounting for over 40% of all, many of which of sorts that repair in time; but even omitting these still yielded the rather large neonatal rate of 6.9/1000.) Once again, while the rate of the former far exceeded that of the latter, the proportion of them detected prenatally, 12%, was far smaller than the 54% of the other. A striking increase in the rate of prenatal diagnosis of congenital malformations, made at 18–24 weeks of pregnancy, occurred over the 21 years of the survey, contrary to the finding in another region of France, described above (Klein et al. 1999), which was ascribed to 'dramatic' technological improvement in sonographic equipment. Finally, the possible reservation should be registered that the study was not population based in the ordinary sense of the term, since it was conducted through a malformation registry located in maternity hospitals.

Data regarding a selection of severe congenital malformations diagnosed pre- or postnatally in 1995–9 were the subject of a European population-based multiregistry report (Garne et al. 2005). The total rate of occurrence was 3.6/1000, i.e. about 10% of all such malformations usually ascertained. The cardiovascular malformations reported were limited to transposition of the great arteries and hypoplastic left heart, and the rate of their combined occurrence was 0.5/1000; while the rate of neural tube defects–the usual anencephalus, spina bifida, and encephalocele–was 1.0/1000; and were prenatally diagnosed in 41% and 78% of cases respectively. The latter and other overall figures are largely meaningless however, since in these respects the European regions contributing the data varied widely, and the only positive comment that can be made is that much catching up is waiting to be accomplished.

Similar to the above was a registry-based congenital malformation surveillance in 1981–2000 of the Paris population (De Vigan et al. 2005). The overall congenital malformation frequency was 31.8/1000. That of neural tube defects, 1.0/1000, conformed to that found in a widespread study in France (Alembik et al. 1997), a low-prevalence geographic area. The only cardiovascular malformation data analyzed were that for transposition of the great vessels, tetralogy of Fallot, and hypoplastic left heart, which indicated a frequency of 0.97/1000, very close to that for neural tube defects. Trisomic defects occurred in 3.4/1000 births, with Down syndrome constituting over three-quarters of them. Malformations in the latter were not mentioned.

Scanning at an early fetal stage, 11–14 weeks, for the purpose of gestation dating, perhaps because of this earliness, failed to detect cardiovascular malformations (Cedergren and Selbing 2006). Other structural malformations detected were few as well, 4.8/1000, in a group of unselected women observed prospectively, many of the central nervous system. At birth however these few were augmented by a similar number, which included 3.3/1000 cardiovascular malformations.

## SCREENING OF ATRIOVENTRICULAR SEPTAL DEFECT

Problems associated with this malformation, said to be the most common one detected prenatally, i.e. greater severity of the condition itself and of its associated extracardiac abnormalities, its high fetal mortality rate, prognostic difficulties, etc., call for it to be given special attention.

An early review of atrioventricular septal defect made at Guy's Hospital in London found it in about 8.3/1000 16–36 week old fetuses in pregnancies referred in 1980–6 for various reasons (Machado et al. 1988). In a small number of cases the defect was isolated, many others had Down syndrome. In cases referred because of family history, in none was the previous defect an atrioventricular septal defect. Many severe cases were aborted, others died pre- and postnatally, and few survived, two with Down syndrome.

In Babies Hospital in New York in 1994–8 atrioventricular septal defect was diagnosed prospectively by four-chamber view in about 15% of all fetuses with cardiac defects seen prenatally (Allan 1999). The diagnosis was made at the relatively late mean age of 27 weeks, with a wide range of 15–40 weeks, the only further information regarding time was the statement that in 55% of the cases it was done too late for pregnancy to be interrupted. In almost 90% the defect was complete, in about one-third it was the only heart defect, and almost three-quarters of these had Down syndrome, whether isolated or associated. Half of the cases were aborted, died in utero, or died postnatally. The array of heart defects identified postnatally was said to be similar to that in the fetuses, which may have been related to many of the latter having been examined late in pregnancy. It was calculated that less than half of the occurrences of this defect were detectable prenatally.

A detailed report was made of the findings at Guy's Hospital (Huggon et al. 2000). Retrospective review of hospital records found atrioventricular septal defect listed in 20.4/1000 referred pregnancies, almost all diagnosed prenatally, constituting 17% of all structural defects found. Half of them had no other cardiac defect and 14% a wide variety of significant extracardiac abnormalities. Almost half of those with known karyotypes had abnormal chromosomes, 80% Down syndrome. Difficult to explain, but important for mortality considerations, was the fact, something of the sort noted by other authors, that Down syndrome in cases in which atrioventricular septal defect was the only cardiac abnormality was almost three times as great as in cases with extracardiac abnormalities. The seriousness of this defect was indicated by the small number of cases that survived to term and afterward.

A review of fetal echocardiograms made at health centers in Vancouver in 1985–97 discovered referrals of 12.7/1000 cases of atrioventricular septal defect, diagnosed at a mean age of 26 weeks (Delisle et al. 1999). In over half the cases the defect was isolated, the remainder had other cardiac defects also diagnosed prenatally. Half the cases had Down syndrome, and again the frequency of the isolated defect was significantly greater than those in which the defect was associated with other heart conditions. As for mortality, after excluding pregnancy terminations,

almost two-thirds survived, perhaps even more so in those with isolated cardiac abnormalities, which was a better record than previously reported.

A study in Leeds compared characteristics of the defect in liveborn infants with those in fetuses (ter Heide et al. 2004). In this opaquely written report one had to struggle to excavate some facts. In referrals to a tertiary center in the Leeds area in 1996–2001 atrioventricular septal defect was identified in some undisclosed fraction of prospectively collected liveborn infants, 29% diagnosed prenatally, 53% with Down syndrome. The proportion detected prenatally was not significantly different in those with and without chromosome abnormalities (25% vs 35%). Thus overall, and even in those with Down syndrome, the prenatal detection rate was unsatisfactory.

It is thus apparent that the study of this most common and serious cardiac malformation of fetal life is further impeded by its being poorly detected by the best of tools presently available to obstetricians and cardiologists.

# CHAPTER 14

# SUMMARY TO THIS POINT

What is now known about the totality of the frequency of cardiovascular malformations, uncovered through three-quarters of a century of probings, as lengthily recounted above, can be summarized briefly. The earliest studies, made in school-age children, in the 1920s and 1930s, indicated that less than 1–2/1000 examined children had such defects; the apparently low estimates due to the tools of detection then available being relatively crude and the investigators poorly experienced; but also because, as studies of children of younger ages in time revealed, some number with severe defects died before reaching school age.

With the advent of more refined apparatus and more knowledgable investigators greater frequencies were found, at first of 3/1000 births, and with further advanced diagnostic devices and greater proficiency in their use, estimates were made of 3–6/1000 and even more, often through discovery of many defects, most especially ventricular septal defects, discussed further below, that were less severe and thus less easily detected.

Additional matters often confusing findings were biased ascertainment, and–especially interfering with comparative studies–admixture of noncardiac defects, hereditary and not, appearing in one-quarter to one-third of cases with cardiovascular malformations.

Along the way it was realized that ascertainment of the total load of cardiovascular malformations must consider early loss of some fraction of such defects, through abortion, interrrupted pregnancy, stillbirth, and neonatal death. Findings in spontaneous abortion depended on the age of the specimens, as well as on influencing factors such as chromosomal aberrations and associated conditions. In embryos under 18 weeks of age cardiovascular malformations were noted in 20–30/1000 abortions, but in youngest ones, 12–13 weeks old, greater ones, 48–88/1000, without satisfactory explanation. The numbers were sparse however and difficult to interpret. Estimates in late fetal death and stillbirth were at first modest, about 1/1000 cases, due in part to low autopsy rate. Later findings with larger numbers and closer inspection gave more realistic ones, of 12–18/1000 stillbirths on the low side, and up to 48–120/1000 stillbirths on the high; with overall findings ranging from about 0.6–1.8/1000 births. Interestingly, these findings have been more or less constant over time. Frequencies in neonatal death were much

higher, often 3–5 times higher, sometimes more, than in stillbirths, in studies reporting both. The reason for this, as was occasionally voiced, was puzzling. Still, the total frequency of cardiovascular malformations in abortions and stillbirths, it has been conjectured, may be five times that in live births (Hoffman 1995).

It can be summarized that in live births, about which there is by far the most complete and reliable data regarding the frequency of cardiovascular malformations, the present judgment is that it may be as great as 8/1000; but that about half this number consists of minor anomalies of little or no medical consequence, a large fraction of the most common of which, ventricular septal defects, close spontaneously by the end of the 1st year of life.

At the end of the day, it becomes clear that attaining the goal of estimating what in the course of life, from embryo to childhood, is the load of malformations of the cardiovascular system, is asymtotic. This never quite getting there is illustrated and emphasized by the intractable differences between studies at different times and places, amounting to barriers of comparability to yielding consensus; matters considered in depth by Ferencz and colleagues (1990). One may yield to pessimism, and go along with their heartfelt "why measure congenital heart disease prevalence?", but like them consider that striving for answers to this as for other human problems is–in my words–its own reward.

CHAPTER 15

# VENTRICULAR SEPTAL DEFECT

## INTRODUCTION

In virtually every publication dealing with congenital cardiovascular malformations the most frequent of the many types reported has been ventricular septal defect. This fact, of great interest in its own right, calls for closer inspection. The statistics of this phenomenon, its forms, how often it occurs, its fate, comprise the subject of this section. This defect was first noticed in the mid-19th century, as mentioned by Abbott (1932), but for a time seen only in adults, until found in children early in the 20th century (Wade and Wright 1963). Not for many years however were attempts made to learn how often it occurred. As was seen with respect to cardiovascular malformations in general, this undertaking has been beset by various difficulties, whether in livebirths–newborn or older children–or deaths. It is best first to consider findings in the last.

## IN DEATHS

Ventricular septal defects, like cardiovascular malformations generally, are more often found in deaths–induced and spontaneous abortion, stillbirth, neonatal–than in surviving livebirths. In considering what is known of the defect in the former, we see that details of findings especially in abortion have been scanty.

## IN INDUCED ABORTIONS

In abortions induced in Japan for social reasons ventricular septal defect was found in 7.8/1000 externally normal specimens at about 6–8 weeks of gestation (Semba 1975). This frequency, which is as great or even greater than the largest neonatal estimate (with certain exceptions noted above), may have been due to delayed closure (see below for discussion of this phenomenon) in some of the older embryos, as is the case at postnatal ages. Microscopic examination of a larger number of specimens of this age revealed a still greater frequency of this condition, 38.6/1000, comprising 76% of all heart anomalies (Takano et al. 1976). No further studies from this exotic source have been found; thus this seems to be the sum and substance

of knowledge of the 'normal' prenatal level of ventricular septal defects, if that is what such abortions represent.

## IN SPONTANEOUS ABORTIONS

A summary report of studies from Vancouver hospitals, in general discussed above, of conceptuses spontaneously aborted before 20 weeks of gestation (Poland et al. 1981), noted that focal cardiovascular defects were not found in embryos, i.e. in those less than 10 weeks of age. In older ones, fetuses of 10–20 weeks of age, ventricular septal defect was the commonest heart defect, with a frequency of 32.0/1000. But this was of heart plus associated defects, while that of ventricular septal defect alone was 4.9/1000. Thus 85% involved multiple defects, associated with other cardiovascular malformations only or with heart and noncardiac defects, including 11.1/1000 with Turner syndrome. Down syndrome was not mentioned. A report from nearby Seattle was not more informative, finding 8.0/1000 at 2–18 weeks of age (Shepard et al. 1989).

## IN SCANNED FETUSES

As an aside, we may consider the frequency of the condition, not in prenatal deaths but in scanned fetuses. In pregnancies in England ultrasound scanned at 16 weeks, though the number with the defect was not noted, it was said to be far less common than in infancy (Allan 1989); and similarly in New Haven it was less often detected by echocardiography in fetuses than postnatally (Friedman et al. 1993b).

Nor were findings in routinely examined unselected subjects more productive. Four-chamber scanning at 18 weeks of gestation in Norway detected only one instance of ventricular septal defect (and that not an isolated one), for a frequency of 0.08/1000 fetuses, 1.4% of the total diagnosed postnatally (Tegnander et al. 1995). Almost uniformly, prenatal studies continued to find low frequencies. In Atlanta it was 0.12/1000 livebirths, increasing from 2% of all malformations diagnosed prenatally in 1990 to 11% in 1995 (Montana et al. 1996). In supposedly nonselected patients in Michigan scanned from week 14 onwards the frequency detected prenatally was 0.68/1000 fetuses, while about the same number was undetected (Kirk et al 1997). A small frequency, 0.10/1000 fetuses, was found at 10–14 weeks in a study in England of nuchal thickness as an indicator of cardiac abnormality (Hyett et al. 1999). A similar small prenatal finding, 0.06/1000, was reported from 20 European registries, only 7% of the total detected pre- and postnatally (Garne et al. 2001). This paltry rate of detection in unselected scanned fetuses must mean, puzzlingly, that the defect largely evades prenatal diagnosis.

## IN STILLBIRTH AND OLDER AGES

A number of reports were made of the frequency of the defect at various natal and postnatal ages: in stillbirths, i.e. late fetal deaths, 22.6/1000 (Hoffman 1968), 6.7/1000 (Mitchell et al. 1971a); in neonatal deaths, 11/1000 (Ober 1955), 2.9/1000

(Lambert 1966), 8.4/1000 (Mitchell et al. 1971a); in live births, 0.22/1000 (Esscher et al. 1975), 0.15/1000 (Kenna et al. 1975); in infant deaths, 115/1000 (Carlgren 1959), 21.3/1000 (Landtman 1971); in stillbirths plus infant deaths, 6.2/1000 (Busch et al. 1985), 7.6/1000 (Abu-Harb et al. 1994); to age 5, 23.6/1000 (Hay 1964), 137/1000 (Laursen 1980).

Though these numbers overlap considerably, clearly the frequency of ventricular septal defect in early death is about 15–20 times that in survivors.

## IN LIVE BIRTHS

The initial avenue of determining the dimensions of the question, as was the case for all cardiovascular malformations, were population-wide studies, because no other was feasible at the time. In the earliest ones, of children of elementary and high school age, the frequency, based on clinical signs, i.e. auscultation, as was predominantly the mode at the time, was low, 0.5–0.9/1000 (e.g. Rauh 1939, Mustacchi et al. 1963, Rose and Keith 1966), and even lower, 0.2/1000, in male college students (Perry et al. 1969). In these instances the defect usually constituted about 30–45% of all cardiovascular malformations. Many later studies were made of wider age spans, from birth to older childhood ages, which on the whole yielded greater frequencies, in more recent ones 1.9–2.8/1000, but which on the contrary comprised a smaller proportion of all, about 20–35% (e.g. Feldt et al. 1971, Fixler et al. 1990).

Studies centered on hospital births were soon turned to, well defined subjects providing more secure information than diverse populations. In the very few that were limited to newborns the frequency was usually 1.4–1.9/1000, about 35–45% of all (e.g. Hoffman and Rudolph 1965, Calzolari et al. 2003). Many more studies however were of infants up to 1 year of age, which mostly found frequencies of 0.6–1.0/1000, but occasionally as high as 2.0–3.0/1000, mostly about 24–35% of all (e.g. Richards et al. 1955, Wren et al. 1999).

It is to be recognized that the frequency reported in some earlier studies was undoubtedly inflated, no doubt because isolated and associated defects, cardiac and noncardiac, were lumped together (e.g. Richards et al. 1955, Mitchell, et al. 1971a, Hoffman and Christianson 1978). In some studies, especially more recent ones, there was a different reason for larger discovered frequencies: the increasing additional detection of smaller, less severe defects, even before but especially after sophisticated echocardiographic equipment began to be used in the 1980s (e.g. Bound and Logan 1977, Fixter et al. 1990, Bosi et al. 2003).

Furthermore, with the introduction of noninvasive echocardiographic procedures, frequencies diagnosed by these and at times by older invasive methods–detecting less severe and more severe forms of the defect respectively–could be reported individually. For example, a Baltimore study found the defect in 0.34/1000 livebirths by the first method and 0.86/1000 by the second (Ferencz et al. 1985). Corroboration of this distinction soon came from Alberta and Texas (Grabitz et al. 1988, Fixler et al. 1990), which in addition, as mentioned above, reported that frequencies found

by the noninvasive method had increased year by year. In a Seattle study in 1981–6 more sensitive echocardiographic techniques found an even greater frequency, 4.7/1000 live births (Moe and Gunderoth 1987).

Several studies noted remarkably high frequencies of the defect. In a hospital in western Israel color Doppler echocardiographic screening of consecutively born neonates identified a frequency of muscular ventricular septal defects of 53/1000, all asymptomatic (Roguin et al. 1995). The great majority were isolated and in those followed up for 6–10 months 89% closed spontaneously. Risk of the defects was not associated with numerous environmental and familial factors. The same procedure was followed in studying liveborn premature neonates born in 1995; in whom however the rate of closure was not different than in a group of full-term ones (Du et al. 1996).

A similarly high frequency of ventricular septal defects, 44/1000, the great majority small muscular defects, was detected by echocardiography in clinically normal low risk neonates in Belfast in 1994–8 (Sands et al. 1999). The infants were apparently not followed to learn in how many the defect closed. The only comment made about this finding was that it was "much higher than might be expected [especially since] 'high risk' infants were excluded."

Can these extraordinarily high frequencies be explained, at least in part, by being found in newborns, at an early stage of the normal closure process, as postulated years ago (Mitchell et al. 1967)? The very high proportion spontaneously closing, as discussed below, would support this possibility.

## VENTRICULAR SEPTAL DEFECT TRENDS

The frequency of ventricular septal defects has been on the rise for some time. Reports, especially of the isolated form, had indicated an undoubted increase in its occurrence. But this was not entirely new. For example, Carlgren (1969) in Sweden noted an increase in 1941–60 from 1.9 to 3.2/1000; and Bound and Logan (1977) in England, a doubling from 1.1 to 2.2/1000 in 1957–71; but while the latter had no explanation, the former conjectured it was due to an increase in small defects not easily diagnosed in the earlier years. And similarly in Atlanta the defect grew significantly in 1968–75 from 1.1 to 2.1/1000 live births (Anderson et al. 1978), and continued to do so in the several following years (Pinkley and Stoesz 1981). Across the Atlantic in England the number of cases quadrupled yearly from 1985–97 (Wren et al. 2000), and in Italy it rose in 1980–2000 from about 1.6 to 2.3/1000 live births (Bosi et al. 2002).

What accounted for this widespread trend? Possible explanations were offered for the sharp increase seen in a nationwide survey in 1970–7, which in Atlanta reached 2.5/1000 live births (Layde et al. 1980). If it were real, it was hypothesized, the increase might have been due to: an epidemic caused by a newly introduced teratogen, to a change in perinatal care, or to improved diagnosis. If the last, reasoning continued, the increase must be due to better detection of minor defects, of the sort that largely close spontaneously by 1 year. While the expectation was

correct that at this age the proportion closed should be the same after as before the reported increase began, the overall increase in prevalence remained. Further, the frequency of severe defects, i.e. those least likely to be overlooked at diagnosis, increased at the same pace as did minor ones. Thus better identification as an explanation of the increased frequency was found not to be possible.

A similar pattern seen in a study in the Albany, New York area led to a different conclusion (Spooner et al. 1980). Isolated ventricular septal defect diagnosed under 1 year of age rose from 0.9/1000 live births in 1970 to 4.8/1000 in 1982, the rise in those of the mildest degrees being proportionately even greater, while that of more severe forms remained fairly stable during the period. This and other lines of evidence thus supported the view that the increase was due to changes in methods and criteria of diagnosis of sorts of the defect that had seldom been detected previously, leading to increased detection of minor degrees of the defect.

The question–epidemic or improved diagnosis?–was also asked by a Baltimore-Washington study (Martin et al. 1989). A 60% increase in such defects had been noted in 1981–4, so great indeed that it accounted for the entire increase in the level of all congenital cardiovascular malformations in the period of the survey. The increase was limited moreover to isolated defects, as confirmed by echocardiography. Thus the epidemic explanation was excluded, since the increase could be wholly imputed to improved ascertainment.

In a study in Norway the same was discovered, that the increased frequency of all cardiovascular malformations in 1982–91 was entirely due to the increase of ventricular septal defects (Meberg et al. 1994). The defect had risen during this period from 4.0/1000 live births to 6.5/1000, i.e. before and after echocardiography was available; during which the frequency of virtually no other heart malformation, including atrioventricular septal defect, had increased,. Thus again improved ascertainment was the entire explanation of the increase in the ventricular septal defect.

## VENTRICULAR SEPTAL DEFECT CLOSURE

What might this increasing frequency have meant for closure of the defect? In the embryonic heart the opening or foramen between the left and right ventricular cavities becomes obliterated by formation of a wall whose upward growth, separating the ventricles, is normally completed 6–7 weeks after conception. In some embryos the closure fails to occur at the usual time, and it remains open, resulting in what is called a ventricular septal defect. In such cases closure may happen later, in prenatal or even postnatal life. When and how often this takes place has occupied many studies, which found a wide range of rates and ages of its occurrence (Hoffman 1987).

It was not too long ago that spontaneous closure of isolated ventricular septal defects, especially of the muscular portion, the most common of these states, was discovered to be fairly common, almost to be physiological. Thus the defect is rare in adults, uncommon even in children more than 2 years old (Rose and Keith 1966), since in many cases closure occurs by 1 year of age. The closure is usually

monitored, even at present, by a clinical sign, a sound–a systolic murmur–by which the defect is usually revealed, and also by which its disappearance in time is learned.

This gradual closure was first clearly detected by repeated cardiac catheterization (Evans et al. 1960). In a group of otherwise apparently healthy children seen in a Toronto cardiology clinic from 1949–59, most of whom were first examined before 1 year of age, closure occurred in about 31% of them. And 10 years later it was about the same, 25% (Li et al. 1969).

The mechanism of true anatomical closure is still not clear; the means by which this process may take place were outlined earlier and also more recently (Wade and Wright 1963, Moe and Gunderoth 1987). Infant size was an acknowledged critical factor, but whether immaturity or prematurity was more important was a matter of dispute, some finding that closure was as frequent in premature as in term infants (Hoffman and Rudolph 1965), that premature infants had the defect more often than term ones (Moe and Gunderoth 1987), and others that it was not prematurity per se that affected closure (Mitchell et al. 1971a). The finding that those with isolated ventricular septal defect were undersized at birth and also gestationally younger than a comparison group suggested that closure is a continuous process throughout pregnancy, which may have accounted for its not being complete at birth (Mitchell et al. 1967).

The rate of closure differed, sometimes according to length of follow-up. In earlier studies, in births in Sweden in 1951–60 it ranged from 18% in the first few years of life (Carlgren 1969), to 33% at ages 7 months to 1 year, mostly of small or medium-sized defects, in infants followed from birth in hospitals in New York City in 1960–4 (Hoffman and Rudolph 1965).

The frequency and time of closure were established more precisely in infants with clinically diagnosed small ventricular septal defects seen at a cardiac clinic in Baltimore in 1967–9 (Alpert et al. 1973). In all, closure occurred in 58%, at a mean age of about 2 years, in 65% and 25% of those with muscular and membranous defects respectively. The earlier the age of diagnosis the greater the closure rate, over half diagnosed soon after birth closed by 5 years of age, etc., with the expectation that almost all the remainder would close "eventually;" a prediction vindicated by a greater than 10-year follow-up (Alpert et al. 1979). There was no attempt to explain the larger closure rate than had been found by others. Only the standard diagostic tools of the era had been used.

The use of newer devices led to detection of unusually high rates of closure. A pediatric cardiology clinic in Seattle found isolated septal defects closed in 46% of infants born in 1981–6 followed from birth, the great majority in the 1st year; again significantly more often in muscular than membranous defects, but also not significantly different in premature and term births (Moe and Guneroth 1987). The high rate, imputed to diagnosis by pulsed Doppler echocardiology, was perhaps related to the no doubt spuriously high freqency of ventricular septal defect, 4.7/1000 live births.

Doppler color flow echocardiography also detected high rates of ventricular septal defect closure, predominantly of the muscular form, in various other regions, an

eastern area of Germany (Trowitzsch et al. 1990), in Japan (Hiraishi et al. 1992), and in Denmark (Garne 2006).

Similar patterns were seen in Florida in a study of patients with ventricular septal defects in 1979–97, in which 71% closed spontaneously, but only after lengthy follow-up, and in most only after diagnosis by Doppler flow apparatus became available (Krovetz 1998). The frequency of ventricular septal defect was also high, about 5.6/1000 live births, in a prospective study of infants in the Tennessee-Virginia area in 1986–90, in which Doppler flow diagnosis detected closure in 41% of the muscular defects and 24% of the membranous ones at the end of 1 year, and in 79% and 42% respectively at the end of 5 years (Mehta et al. 2000).

High rates of muscular ventricular septal defects and of its closure were found in consecutive neonates in a hospital in western Israel (Roguin et al. 1995, 1998). The frequency of isolated defects, as determined by color Doppler echocardiography, was 47/1000 live births, and as followed up for 1–10 months the rate of spontaneous closure was 89%. In accord with other findings, in the study's limited number of subjects, the rate was not higher in preterm than full-term infants (Du et al. 1996).

High closure rate was also found in a study in Norway (Meberg et al. 2000). Most of the ventricular septal defects were apparently of a minor degree, since over a quarter of them closed by 6 months, 70% by a year, and the remainder later. Of them all 82% were muscular, with spontaneous closure occurring in 74% of them. Indicative of the relation between the rate of the defect and the rate of its closure was the fact that the fraction that closed in the later years of the survey was significantly larger than in the earlier years.

Septal defects, ventricular and atrial, in births in Funen, Denmark in 1986–98, reported by a congenital malformation registry, were followed to determine closure patterns (Garne 2006). Diagnosis was made in children examined periodically up to age 5 years. The frequency of ventricular and atrial defects was 2.7 and 1.1/1000 live births respectively. Of the former somewhat more were muscular than membranous, 55% vs 45%, and more of the muscular were isolated than the membranous, 93% vs 76%. Closure of the membranous defect proceeded slowly, increasing from 5% at 1 year to just under 20% at 3 years, and barely increasing further; while closure of the muscular defect rose steadily from about 23% at 1 year to 65% at 5 years. These and other differences between the two forms seemed to indicate individual etiological bases.

Clues to the relation of ventricular septal defect frequency and ventricular septal closure rate, both of which seem to increase in tandem, were partly supplied by the Albany study described above (Spooner et al. 1980), in which it was noted that the spontaneous closure rate increased with earlier diagnosis of the defect, allowing more time for closure to occur.

It is of interest to recall an incidental finding, that ventricular septal defects closed spontaneously by 5 years or more of age in only in a small minority of Down syndrome patients, the infrequency attributed to most of the defects being large (Noonan 1978).

CHAPTER 16

# CARDIOVASCULAR MALFORMATION AND DOWN SYNDROME

## INTRODUCTION

Chromosomal aberration is the commonest maldevelopmental state associated with serious cardiovascular malformation, and of their several types the most frequent is Down syndrome, trisomy 21 (Warkany et al. 1966, Polani 1968, Eskedal et al. 2004).

We can take a small break to talk about what has come to be called Down syndrome. The 'discoverer' of the disorder, the London physician John Langdon Down, in a short paper published in 1866, called it the "Mongolian type of idiocy." In a few words he described it and wondered about its causation: "Had the nurse dosed the child with opium? Has the little one met with an accident?" But no, he asserted, "they are always congenital idiots and never result from accidents after uterine life." From the time it was thus called Mongolian idiocy its name has metamorphosed from Mongolism to Down syndrome to trisomy 21, the latest designation, following the discovery of its cytogenetic etiology almost 100 years after Down's paper appeared in print (Lejeune et al. 1959). It is called Down syndrome here.

Many different congenital malformations occur in Down syndrome (Carter and MacCarthy 1951, Torfs and Christianson 1998), but especially frequent is heart defect; a fact abundantly documented in the later years of the 19th century; e.g. by the physician Garrod (1899), subsequently famed for his contributions in many medical areas. While cardiovascular malformations also occur fairly often in other chromosomal aberrations, Down syndrome differs in this respect, both qualitatively and quantitatively; a feature that has been an intensive area of study, if only because of its close tie to infant mortality.

The observation that cardiovascular malformations of various sorts were common in Down syndrome continued into the earliest years of the 20th century. There was little consensus about their frequency however, the wide range reported being attributed to variable diagnostic criteria and differences in age distribution, death rate, and subject selection (Berg et al. 1960).

Cardiovascular scholars such as Maude Abbott and Helen Taussig had emphasized that of this variety of heart defects one occurred so frequently as to be

considered highly correlated with Down syndrome (cited by Evans 1950, Liu and Corlett 1959). This particular cardiac defect has had a number of names over the years: persistent ostium atrioventricular commune, as it was sometimes earliest known; also endocardial cushion defect, atrioventricular canal, atrioventricularis communis, and complete atrioventricular canal. At present it is most frequently called atrioventricular septal defect (Becker and Anderson 1982, Anderson et al. 1984), denoting simultaneous defect of the atrial and ventricular septa plus abnormalities of tricuspid and mitral valves.

## A LARGELY CHRONOLOGICAL ACCOUNT

Not everyone supported the idea of the affinity of this defect for Down syndrome, e.g. Evans (1950). In his summary of findings of autopsies of cases of mongolism–as he called the condition–dying in the 1st month to 7th year of age in 1911–49 at the Hospital for Sick Children in London, he noted that in the 44% of cases with cardiovascular malformations 14% had this peculiar defect, while a larger proportion had ventricular or atrial septal defect. He felt therefore that the 'peculiar' defect "should not be regarded as the typical cardiac lesion of mongolism"; this despite its absence in patients without Down syndrome. It should be mentioned that more than twice as many Down syndrome patients with cardiovascular malformations died in infancy as those without them.

A later study of Down syndrome cases, admitted to a different London hospital in 1944–58, supported Evans' doubt (Liu and Corlett 1959). Of the cases still alive at the time of the report, with a mean age of 10 years, 9% had cardiovascular malformations, while 36% of those that had died had such defects, the mean age at death of those with and without defects almost being identical. In both survivors and nonsurvivors atrioventricular septal defect was far less frequent than ventricular and atrial septal defects.

Doubt of this 'special place' continued for some time. In his epic tome Congenital Malformations: notes and comments, Warkany (1971, p 576), based on a large number of autopsies, said that, even though atrioventricular septal defect occurs more often in Down syndrome than in non-Down patients, there "is no cardiac malformation that is typical of mongolism." By which he may have meant that the defect is not exclusive to them. The question what is "typical" becomes philosophical and beyond the bounds of the present work.

The tide started turning a bit earlier with a study of autopsied Down syndrome cases from 1947–58 collected from obstetric and pediatric hospitals and a mental facility in England, the majority less than 1 year old (Berg et al. 1960). A large proportion had cardiovascular malformations, 56%, as diagnosed by the methods of the day, two-thirds, excluding stillbirths, dead in the 1st month. The defects in the Down syndrome cases were compared with those in mentally impaired autopsied individuals in the same institutions without Down syndrome. The latter had as wide a variety of cardiac defects as the cases, but a smaller frequency of isolated

atrioventricular septal defect, 6% vs 20%. The belief of earlier observers in the special place of this defect in Down syndrome was thus strengthened.

The fact has continued to be unquestioned for the last 50 years or more, that of all the different types of heart defect, the most common one in Down syndrome is almost invariably atrioventricular septal defect; in contrast with the picture in all children, in which it is one of the least frequent, usually 2–3% of all cardiovascular malformations in liveborns, 5–7% in stillborns, and somewhat more in neonatal deaths. The preponderance of this defect in Down syndrome gives it a special place, but one that is far from exclusive to this syndrome.

In hope of a sharpened inquiry, a prospective study was made of a large number of relatively unselected children with Down syndrome, of predominantly younger ages, mainly referred for counseling to a Toronto hospital in 1955–7 (Rowe and Uchida 1961). In this group ventricular septal defect and complete atrioventricular septal defect were about equally frequent, 33% and 31% respectively; but in autopsied cases the atrioventricular septal defect was the more common, 28% vs 17%, almost three-quarters dying by 1 year.

The relation of mortality to heart defect was made explicit by a summary of numerous studies of congenital cardiovascular malformation associated with cytogenetic aberration (Polani 1968). It found that heart defect in Down syndrome was over twice as frequent in diagnoses made in autopsies (53%) as in clinical ones (23%). The survey also revealed that atrioventricular septal defect, unassociated with other cardiovascular malformations, was apparently specific to Down syndrome, not having been found in other autosomal trisomies.

The point regarding mortality was also made by a British Columbia registry study of handicapped children and adults of unstated ages in 1955–60, which showed that the frequency of cardiovascular malformations in live Down syndrome individuals was 8.3%, while in dead ones it was 33.3%, compared with 0.8 and 3.3% respectively, in non-Down mental patients (Renwick et al. 1964). The mean age of mothers of Down cases was 33.7 years compared with 27.0 for all mothers in the registry. Heart defect type was not listed.

A study in Minneapolis noted a multiplicity of cardiovascular malformations in autopsied Down syndrome patients (Tandon and Edwards 1973). About half were under 1 year of age, and of these 37% had complete atrioventricular septal defect, not much more however than the 32% that occurred in older ones. Ventricular septal defect was the next most common type, but only a small proportion of them closed spontaneously, and that not till an advanced age. Another pertinent finding was that patent ductus arteriosus was present in almost half of cases older than 1 month.

A large number of infants and children with Down syndrome were seen in 1962–73 in a Boston hospital, 62% with cardiovascular malformations, the high level perhaps related to the 33% overall mortality rate (Greenwood and Nadas 1976). The predominant defect was complete atrioventricular septal defect, at 23%, with another 6% incomplete, the former with a 52% mortality rate at a mean age of 29 months; which was more than twice that of the next most common defect, ventricular septal defect.

Examination by echocardiography of infants with Down syndrome born in a Belfast hospital in 1987–9 presumably gave definitive data regarding frequency, etc. (Tubman et al. 1991). Forty-two percent had cardiovascular malformations, about two-fifths of them atrioventricular septal defects. Compared with other diagnostic methods echocardiography proved to be 100% specific.

Two registry-based studies in Atlanta examined the occurrence of cardiovascular malformations in Down syndrome. One, of births in 1968–80, based on numerous sources of ascertainment, found an overall heart defect frequency of 33% (Khoury and Erickson 1992). The most common defect, listed as endocardial cushion defects (i.e. atrioventricular septal defects, apparently associated or not with other defects), was recorded in 52% of affected cases, with patent ductus arteriosus, atrial septal defect, and ventricular septal defect following. All defects markedly increased during the years surveyed, attributed to improvements in diagnostic radiology, especially increased use of echocardiography. These shifts were contrasted with the relative stability of gastrointestinal defects in Down patients. Age at diagnosis was unknown and not considered was its relation to mortality. A number of associations were discovered: the frequency of cardiovascular malformations was four times greater in liveborn infants than stillbirths, greater in preterm than term infants, etc. It is unfortunate that such associations were neglected with regard to atrioventricular septal defects.

A later study, in 1989–95, in the Atlanta area of Down syndrome livebirths, little overlapped the previous one (Freeman et al. 1998). In these cases 44% had cardiovascular malformations, almost half with atrioventricular septal defect, isolated or not. Patent ductus arteriosus was far less frequent than in the earlier one (7% vs 38%), due of course to the former largely being based on newborn records and the later on cardiac evaluations after initial hospital discharge. It is notable that the maternal age of Down patients was unrelated to the heart defect frequency, and that maternal race was of no significance in this respect, again differing from the greater frequency of cardiovascular malformations in black than white infants reported in the earlier Atlanta report. The overall frequency of Down syndrome was 1/1000, significantly less than that found in a comprehensive search in metropolitan Atlanta (Rasmussen et al. 2006).

The occurrence of major congenital malformations in Down syndrome infants was analyzed in three European hospital-based registries, Italian, French, and Swedish (Källén et al. 1996). In cases born in 1976–9 the most common malformations were those of the heart and great vessels, with an average frequency of 26%, somewhat less than often found; in the admittedly few stillbirths only 18% had a registered heart defect. As elsewhere, all three programs noted a "strong increasing trend" in the later years of the survey, the result of improved ascertainment. The commonest defect was atrioventricular septal defect, at about 42% in France and Sweden and 28% in Italy. An increase in overall malformation rate was noted for the last several years of the survey, no doubt the result of improved ascertainment.

It is difficult to justify the lumping together of these findings so dissimilar in a number of respects, ascertainment basis, completeness of reporting, follow-up time,

malformation coding, populational variability in genetic background and numerous other factors, making other than generalizations of little value.

The frequency recorded by the European registry is to be compared e.g. with that in newborns with confirmed Down syndrome in an Alabama hospital in 1988–92, almost half found to have cardiovascular malformations, the apparently high rate presumably due to the infants being diagnosed by echocardiography (Wells et al. 1994). The commonest once again were atrioventricular and ventricular septal defect, both mostly isolated. The majority with ventricular septal defect required surgery, perhaps because the defect was larger than in non-Down children, as Noonan (1978) had commented. Racial difference in defect frequency was not mentioned, although one-third of the sample was black.

Down syndrome infants who had congenital cardiovascular malformations confirmed by various means were examined in hope it seems of better defining the relation between the two (Shaher et al. 1972). In an Albany, New York hospital in 1967–70 three-quarters of a relatively small number of such children, aged 1 day to 14 years, had multiple heart defects. In the reverse of the usual pattern ventricular septal defect was more common than complete atrioventricular septal defect, 46% vs 28%. About one-quarter of the cases died in infancy, and over one-third of the atrioventricular septal defects and one-sixth of the ventricular septal defects were found in autopsies.

A retrospective study investigating the concurrence of Down syndrome and cardiovascular malformations concerned all patients referred to hospitals in Baltimore and Pittsburgh in 1964–72, of ages from newborn to 24 years old, only one-third under 1 year of age (Park et al. 1977). This sample conformed to the usual distribution of heart defects in Down syndrome, with the greatest number, 43% possessing atrioventricular septal defect, and ventricular septal defect behind at 32%. Three-quarters of the former and 62% of the latter were free of other cardiovascular malformations. In addition 20% of all patients had other malformations, mostly of the gastrointestinal system.

A number of studies turned things around and examined the frequency of Down syndrome in children with cardiovascular malformations. For example, a study made in 1963–74 in a Danish hospital found that 5.3% of children with cardiovascular malformations had Down syndrome and over half of the latter had cardiovascular malformations (Laursen 1976). This sample had an unusual distribution of defect types: ventricular septal defect was the most common, at almost 50%, with common atrioventricular septal defect trailing far behind, at 19%; a statistic at odds with the latter being most frequent defect in a Danish population study of Down syndrome (Mikkelson et al. 1990). Over 84% of the cases had multiple cardiovascular malformations; other associations were not mentioned. About one-third of the children died in the 1st year, mostly of pulmonary complications and cardiac failure, but the defects in the dead and surviving were not detailed separately.

The Washington-Baltimore infant study also turned things around, and found that of the approximately 13% of infants born alive in 1981–6 with chromosome abnormalities 81% had Down syndrome (Ferencz et al. 1989). The most common

heart defect, at 48%, was complete atrioventricular defect, a defect absent in the instances of other chromosome abnormality types. The birthweight of the Down cases was not mentioned, but patent ductus arteriosus was noted in relatively few of them, 3.2%.

In a variation of the above, several studies began their investigation, not by learning how many individuals with Down syndrome had atrioventricular septal defects, but by identifying patients with atrioventricular septal defects and ascertaining how many of them had Down syndrome. One of them, conducted in the university hospital in Gothenberg, Sweden analyzed consecutive occurrences in 1970–96 of complete atrioventricular septal defects, using 2-dimensional echocardiography and color Doppler, available respectively since 1983 and 1990 (Åmark and Sunnegårdh 1999). The use of the latter method was associated with a great increase in the annual number discovered; and this may have been the basis of the high frequency, 85%, of Down syndrome in them. Over half the patients had associated cardiac and noncardiac defects.

A study in Rome also began by identifying patients with atrioventricular septal defects (Marino et al. 1990). Of those with the complete form, 62% had Down syndrome and another 28% the partial form. These facts were in contrast to the instances of the defect in non-Down persons in whom the partial form outnumbered the other. Contrariwise, the defect in Down syndrome cases was significantly less often associated with other cardiovascular malformations than were non-Down ones. The ages of the subjects, unfortunately, were not mentioned, nor how many were examined postmortem.

In a retrospective study of all atrioventricular septal defects identified in Northern Ireland in 1990–9 isolated instances of the defect were diagnosed in 54% of Down syndrome patients at a median age of 3 days (Dunlop et al. 2004). Notable were the findings that Down syndrome individuals were slightly immature and premature, being born at a median time and weight of 38 weeks and 2920 g, and non-Down cases at 39 weeks and 3210 g.

The forms and associations of atrioventricular septal defects were analyzed in a population study of large number of subjects with cardiovascular malformations diagnosed in 1981–9 (Carmi et al. 1992). Atrioventricular septal defects comprised 7.7% of all heart malformations, a higher frequency than usual; over three-quarters of them associated with Down syndrome. This high level, it was speculated, suggested a different developmental mechanism than for the isolated one, as postulated e.g. by Kurnit et al. (1985).

A later analysis hoped to provide evidence for this supposition, by identifying risk factors that distinguish the complete from the incomplete form of the defect (Loffredo et al. 2001a). As in other studies, a far smaller frequency of extracardiac defects occurred in the complete than the incomplete form, but on the contrary a significantly larger frequency of Down syndrome in the complete than the incomplete form. No discernable difference in risk factors was identified however; and a procrustean attempt to implicate pregestational maternal diabetes in some types of the defect was hardly convincing.

Another distinction, term versus preterm birth, was examined in a Newcastle study in 1987–2001 of children born with Down syndrome (Tanner et al. 2005). One-quarter of them were preterm, but the frequency of atrioventricular septal defect was exactly the same in them, 16%, as in those born at term. An earlier report from this area found that about two-thirds of infants with this defect had Down syndrome and the frequency of the defect in Down syndrome was 48% (Wren et al. 1999).

A retrospective study in 1994–8 in Mexico City of Down syndrome births identified through the national pediatric institute had unusual findings (Figueroa et al. 2003). A large proportion, 58%, had cardiovascular malformations, three-quarters isolated; the high frequency attributed to identification through a referral center. The commonest abnormalities were ventricular and atrial septal defect, while very few, 8.7%, had the usually most common atrioventricular septal defect. Thus a considerably different assortment of defects was found than seen elsewhere. Whether this may have been related to the fact that fewer than half the cases had regular trisomy 21, deviating markedly from the usual 95% of that variety, was not considered; reflecting this discrepancy was the fact that cases were mainly born to young and primiparous mothers.

Giving the findings more credibility however were similar ones reported from another Latin American country, Guatemala, where atrioventricular septal defect was also relatively uncommon in Down syndrome cases evaluated in 1997–2003, far less so than ventricular and atrial septal defect (Vida et al. 2005). The meaning of this similarity, genetic or otherwise, bears consideration.

Another apparently disparate finding came from a population study of live births in 1990–4 in Malta (Grech and Gatt 1999). The discrepant finding was that the most frequent heart defect in Down syndrome was ventricular septal defect (most of which were small, no doubt overdiagnosed by sensitive detection methods used), and the next most frequent complete atrioventricular septal defect. The overall frequency of cardiovascular malformations was 8.8/1000, the large proportion also perhaps due to the inclusion of an undisclosed but large number of minor forms of ventricular septal defect; but also possibly to pregnancy interruption being illegal in this nation.

A similar finding was noted in a Chinese population in 1994–5 in Hong Kong, where despite the pattern of cardiovascular malformations being different from that in western populations, individuals with Down syndrome had the same two predominant lesions as occur elswhere, ventricular and atrioventricular septal defect, except that the former was more common than the latter, 38 vs 25% (Jacobs et al. 2000).

Studies have continued from far and near of cardiovascular malformations in Down syndrome, with atrioventricular septal defects found to be the most common or one of the most common of these conditions, far beyond the level in non-Down persons; but with no fundamentally different ideas on the subject (Baciewicz et al. 1989, Venugopalan and Agarwal 2003, Wessels et al. 2004, Abbag 2006).

A nationwide retrospective census was made in Sweden of all occurrences of atrioventricular septal defect in livebirths in 1973–97 (Frid et al. 2004).

The frequency of isolated complete atrioventricular septal defect was 0.19/1000 livebirths, 16% of them in Down syndrome. The distinction between the isolated and complex forms was well demonstrated by 86% of the former in contrast with 37% of the latter occurring in Down syndrome. As operations on the isolated form increased, postoperative mortality greatly decreased, from 52% earlier to less than 10% in the latter years, but was not appreciably different in Down and non-Down patients. Somewhat similar were findings in Iceland, with an atrioventricular septal frequency of 0.23/1000 births and in Down syndrome of 0.64/1000 (Stephensen et al. 2004).

Before moving on, questions asked in recent times regarding the genetic pathogenesis and prenatal development of atrioventricular septal defect may be mentioned and quickly disposed of. It is agreed that compounding the difficulties regarding the association of the defect especially with Down syndrome is its etiological and developmental heterogeneity, and that while at the outset of the present century little with any certainty is known it is promised that further refinements and concepts will advance understanding of its genetic inputs and morphogenesis (Maslen 2004, Blom et al. 2005); which it is to be hoped will be soon forthcoming.

CHAPTER 17

# EPIDEMIOLOGY AND ETIOLOGY OF CARDIOVASCULAR MALFORMATION

## INTRODUCTION

I'll say right here and now that very little is known of the causes of the majority of heart defects, i.e. of the somethings that are responsible for or associated with heart defects coming into being. What these somethings are conjectured to be and what they may possibly consist of are the subjects of epidemiology and etiology.

Epidemiology, as already defined, is the study of "the distribution and determinants of health-related states and events in defined populations" (Last 1988); which in the context of malformations refers to examining whether and how abnormalities, especially particular types, may be related to time, place, circumstance, and condition; for the purpose of clarifying causation, i.e. etiology. Ok, then, as these words say, epidemiology and etiology are intertwined. But they differ, because one examines whether and how a phenomenon, say cleft lip, is associated with variables of numerous sorts that may be of causal significance, and the other identifies direct causes and origins. One may offer clues, the other follows them up (Miller 1969).

What causality is is another matter, debated and categorized since antiquity. As that repository of wisdom, Wikipedia, puts it, "the philosophical concept of causality, the principles of causes, or causation, the working of causes, refers to the set of all particular 'causal' or 'cause-and-effect' relations." Or as Don Quixote's sidekick Sancho Panza put it, in chapter LXVII of the translation of that classic by Peter Motteux, "take away the cause, and the effect ceases."

A neutral definition is notoriously hard to provide since every aspect of causation has been subject to much debate. Most generally, causation is a relationship that holds between events, properties, variables, or states of affairs. Causality always implies at least some relationship of dependency between the cause and the effect. For example, deeming something a cause may imply that, all other things being equal, if the cause occurs the effect does as well, or at least that the probability of the effect occurring increases. It is also usually presumed that the cause chronologically precedes the effect. That's it in a nutshell, a tough one to crack albeit.

It is nevertheless instructive, respecting the challenge of sorting out the respective roles of epidemiology and etiology in elucidating causation, to peruse an article on "etiological factors of congenital heart disease" by Warkany (1960), to see how it was handled in that paper. Following a discussion of theories of pathogenesis of heart defects expounded from the early 19th to 20th centuries, the author introduced the theme of a specific teratogen, rubella, that burst on the scene in the early 1940s. But he then broached a different matter when he said "if we turn now [as he put it] to the other side of the field of etiology . . . we find some, though not overwhelming, evidence for genetic factors at work." In this delicate but pointed way, he gave both 'etiology' and 'epidemiology' their due, and drew the distinction between them that the following pages will expand on. It must be explained that the one term, etiology, has frequently been used to encompass the fields of endeavor of both, and consequently the individual role of each has sometimes been muddled.

## EPIDEMIOLOGY

The basic description of epidemiology is that it is concerned with large numbers of people, groups, populations, contrasted with the study of kinships, families. But the role of epidemiology is best depicted by contrasting it with the role of etiology. Etiology deals with things that precede the phenomena they are imputed to cause, the things being one-time and of brief existence. In contrast, epidemiology is concerned with things that are chronic and thus coincident with the phenomena they are supposedly related to.

The things, usually called factors, that have been considered in epidemiological relation to congenital malformations are many. Included have been maternal age, weight, race, ethnicity; pregnancy interval, birth order, prior abortion; consanguinity; twin studies; fetal sex, birthweight; season, latitude, geography, population density, socioeconomic variables, residential mobility, etc., etc. There have been a plenitude of studies of the association of such elements and heart defects in the second half of the 20th century. But most have only yielded confusing and contradictory findings, with little probing into whatever meaning they may have. We consider only a small selection.

## AN EPIDEMIOLOGICAL MISCELLANY

Several early studies of the association of heart defects with maternal and other characteristics set the pattern for later ones. A favorite defect, patent ductus arteriosus, was noted to be related to one degree or another with a number of features, birth rank, maternal age, sex, season, as well as familial ones (Record and McKeown 1953). Families of children seen at Guy's Hospital cardiac clinic in London in 1947–9 were sent questionnaires which elicited the following information (Polani and Campbell 1955). Birth rank or maternal age was without influence, except for age 40–44, where an increase of tetralogy of Fallot and certain other defects was seen, even when all Down syndrome cases were eliminated, a finding

in strong disagreement with other studies. A seasonal association was found, with a maximum in the spring, but the distribution differed in the sexes.

A study of infants with heart defects diagnosed in 1946–55 at the children's hospital in Paris had mixed findings (Lamy et al. 1957). The sex ratio of the cases as a whole did not differ significantly from that of a randomly chosen control group, but did so for those with a particular defect, patent ductus arteriosus, with, as we learned above, females greatly predominating; while for another, valvular aortic stenosis, it was males that had the greater frequency. Mean maternal age of the whole group was not different from the control, but birth order was significantly higher.

As you can imagine, this did not end these quests. Carried on into recent years, sex differences were found for numerous defect types, one sex predominating in some and the other in others, the one indisputable finding being that atrioventricular septal defect was far more common in females than males (Storch and Mannick 1992, Pradat et al. 2003).

Maternal age and birth order continued to get a great deal of attention, a later study finding that birth order was without influence, but that defects clearly increased with maternal age 35 years and older, perhaps the result of including Down syndrome births (Hay and Barbano 1972). Birth order and infant sex too yielded variable and inconsistent findings, some defects being associated with birth order and others not, some defects being more frequent in one sex and others the opposite (Rothman and Fyler 1976). In one broad study neither sex nor maternal age was associated with any of numerous defects examined (Stoll et al. 1989).

Birthweight is an intriguing subject, but I'm not sure it should be thought to have any causal role, regardless of how nebulous; except perhaps as an expression of fetal growth, or as clue to vague associations. Since it is discussed above it will not be considered further here.

Season of birth, rather than of conception, no doubt because of its ease of determination, was a favorite topic in epidemiological circles, with some defects found to be increased in births at one time of the year or another, but with confusion and doubt, e.g. patent ductus arteriosus more common in winter months in some studies, but only in girls in others (see references in Campbell 1965); all heart defects reported more common in late summer and early autumn in one study (Landtman 1965), but with no seasonal predilection in another (Feldt et al. 1968). Later reports, with no surcease, noted a summer excess, especially of a certain type of ventricular septal defect, as well as a winter excess of patent ductus arteriosus (Rothman and Fyler 1974), and once more no seasonal variation at all (Laursen 1980, Stoll et al. 1989).

Variations in frequency and type of heart defects in racial and ethnic groups were also looked into. In the Baltimore-Washington study heart defects differed in white and black infants, some types being more frequent in whites, others in blacks, e.g. in whites an excess of Ebstein's anomaly, aortic stenosis, etc., and a deficit of pulmonary stenosis and others, with attempts to associate some of the disparities with socioeconomic and other factors (Correa-Villaseñor et al. 1991). Previous studies finding some of these same racial differences were noted.

In Birmingham, England differences between Asian and non-Asian infants were noted, the former (of various national origins) having an overall frequency of 9.4/1000 vs 4.5/1000 in the latter, with the only types differing statistically being patent ductus arteriosus and complex defects more common in the former and coarctation of the aorta more so in the latter (Sadiq et al. 1995). The overall difference was not explained. The only bases of some of the differences considered were consanguinity in Muslims and lower nutritional and socioeconomic status in Asians, which were rejected since these would have impinged on all defects.

Racial differences, almost negligible, were seen in a long-term study in Atlanta, which found a greater overall defect frequency in blacks, 6.6/1000, than whites, 5.9/1000, the excess perhaps mostly due to a small number of defect types (Botto et al. 2001). Racial differences in mortality from heart defects were discussed above (Boneva et al. 2001).

Regarding the association between socioeconomic features and heart defects, I note here only the most recent study of this kind I have located. Using hospital and genetic counseling data in California, it identified infant and fetal deaths in 1987–9 with heart anomalies labeled as conotruncal defects (and isolated orofacial clefts) and examined the association between them and the socioeconomic status of their mothers (Carmichael et al. 2003a). Several such measures, neighborhood and individual–maternal marital status, educational achievement, housing, employment, etc.–suggested an association between low status and increased risk of transposition of the great arteries and a reduced risk of tetralogy of Fallot, but none with orofacial clefts.

Various other such studies were briefly described, from which one can learn that no consistent relation was discovered between measures of socioeconomic status and a variety of heart defects, some reporting no association, others a potpourri of findings, negative and positive. Leading the authors of the paper under discussion to lament "it is unknown why [socioeconomic status] would contribute differentially to the risks of various subtypes of heart defects," and to conclude, with a whimper, as so many others have done over the years, that "replication of the findings of this study is needed before firm conclusions can be reached."

Concluding this section, we recall the comments of an early reviewer, who, critically analyzing an article alleging a higher occurrence of patent ductus arteriosus at high altitude than sea level, expressed doubt, since its possible explanation, hypoxia, was not supported by other evidence (Warkany 1960); a challenge seldom made in later critiques. Seemingly vindicating this cynical comment was a later statistical study, making the same claim, that altitude 3000 m above sea level was associated with certain heart defects, again suggesting, but with no effort to substantiate, hypoxia as a possible cause (de la Cruz et al. 1971).

There is evidence, however, as clear as such things can be, of the relation between elevated altitude and increased frequency of patent ductus arteriosus, the most telling being the gradual increase in the frequency of the defect, following a parabolic curve, with gradual elevation in altitude, such that at levels of 4500–5000 m the frequency is almost 30 times that at sea level (Peñaloza et al. 1964).

## FAMILY STUDIES

This is an area of study that over many years has been given the greatest and most enduring attention, that of the inheritance of cardiovascular malformations. Such studies have taken different forms and have involved various types of situations. They have involved cardiovascular malformations due to single mutant genes, recessive and dominant; those that are part of well defined malformation syndromes of chromosomal, genetic, or nongenetic origin; that occur horizontally in sibs, or linearly, passed on from one generation to another; and have dealt with defects in general or of specific types.

Belief in the familial nature of congenital malformations of the heart was expressed early in the 20th century by Abbott and Debré (cited by McKeown et al. 1953, Johnson 1961), mainly based on evidence provided by isolated families with affected members. Though suggestive, in order to be totally convincing, such evidence needed substantiation by intense family overviews, which were soon forthcoming.

Interest in the heritability of heart abnormalities, oddly, arose almost simultaneously in several localities in midcentury, attesting to the confluence of imagination and opportunity, which upon systematic investigation yielded closely similar findings. A selected sample of the Birmingham population investigated previously by MacMahon et al. (1953) had a frequency of heart defects of 1.8% in sibs born subsequent to the proband, also called index patient, a frequency about six times that in overall births in the interval surveyed (McKeown et al. 1953). Some defects displayed specificity in a small number of fraternities, both the first and subsequent affected individuals having the same defect. In cousins and parents however the frequency was little different than that in the general population.

A great excess of heart defects was also noted in families studied in London (Polani and Campbell 1955). The frequency in sibs born alive before and after the proband was 1.4%; in those later born it was 2.3%, seven times that in the general population. Findings in more remote relations were inconclusive.

A similar study of relatives of probands in a clinic in Paris found a mean frequency of 1.5% in sibs, similar to that in the Birmingham study, varying from 0.5% to 1.9 % for various specific defects (Lamy et al. 1957). None of them however yielded a simple genetic explanation, i.e. the frequency hardly approached that expected of a simple recessive factor. Expanded consideration found no increased frequency in parents, but a complicated calculation appeared to indicate an increased frequency among cousins.

A consecutive series of infants with heart defects diagnosed in a university cardiac department in Berlin in 1951–6 was studied to estimate the relative importance of exogenous and hereditary factors in the occurrence of cardiovascular malformations (Fuhrmann 1961). Certain exogenous factors of possible significance in the etiology of the defects were only slightly more common in the malformed group than in the control individuals, including abortion, trauma, etc. Consanguinity, however, was increased in parents of affected children, and heart malformations were seen

in 2.8 % of sibs, much more than expected, but were rare in parents. Multifactorial inheritance was called upon to explain the findings.

Another study in London of sibs of probands found an increased frequency of several cardiac defects–but not of coarctation of the aorta–varying from 1.1 % in atrial septal defect to 2.7 % in Fallot's tetralogy (Campbell 1965). The overall average was 1.7 %, the same as noted by others, three times that expected by chance, and the same malformation 15–20 times as often as expected. But again no such tendency was seen in parents, with the exception of atrial septal defect, which seemed in some families to display a dominant inheritance pattern.

A series of studies of the familial nature of heart defects began with a report of a large number of patients of a wide range of ages ascertained through university hospitals in Madison, Wisconsin and Montreal (Nora and Meyer 1966). Contrary to other findings a significant proportion, 1.9 %, of parents of probands had heart defects, almost four times that in controls; the proportion of affected sibs was also much larger, 3.3 %; and there was a higher than background frequency in those even less closely related. Ventricular septal defect, the most common defect in probands, occurred in 5.6 % of sibs and 1.2 % of parents, while the next most common, atrial septal defect, was seen in 14 % of sibs and 4.8 % of parents. Increased but lesser frequencies were also found for other defects, but not transposition. Possible reasons given for the differences with previous family studies were thoroughness of interview and survival through surgery into reproductive years, a subject to be returned to below.

In the era of the 1960s there was a surge of interest in the pattern of inheritance of several individual heart defects, with much agreement reported. Studies in London of families with patent ductus arteriosus and atrial septal defect found a defect excess in sibs of probands, with the defects in question quite often homologous (Polani and Campbell 1960, Campbell and Polani 1962). The occurrence of first cousinhood more often than by chance in parents of probands suggested Mendelian inheritance in some cases, especially when the condition recurred in parent and child.

Atrial septal and ventricular septal defects presented complexities that indicated most cases to be multifactorial in origin, i.e. to depend on interaction between genetic and nongenetic components; in some small number of pedigrees, however, inheritance of the former in a simple fashion, i.e. as a Mendelian recessive or dominant, was not precluded (Nora et al. 1967, 1969).

The same indication of multifactoriality was seen in examining the inheritance of other defects: a small but increased frequency in sibs of probands, for transposition of the great vessels (Fuhrmann 1968), atrioventricular septal defects (Emanuel et al. 1968), and patent ductus arteriosus (Wilkins 1969).

A similar analysis was made for three defects in a study in Stockholm, patent ductus arteriosus, coarctation of the aorta, and atrial septal defect (Zetterqvist 1972). The frequency of patent ductus arteriosus in sibs of probands was 2.3 %, this and other features indicating multifactorial inheritance. Another finding worthy of note was that the frequency of all other heart defects in relatives of the probands was

the same as in the general public. The findings for the other two defects generally supported this inheritance type also, but the evidence was not as conclusive as for the first.

An analysis was made of families, selected from a large number of literature reports, in which there were pairs of siblings with heart defects of different types, in the search for evidence of nonrandom association (Fraser and Hunter 1975). An excess of pairs was seen for several combinations, including tetralogy of Fallot plus pulmonary stenosis, transposition of the great vessels, and ventricular septal defect; which suggested developmental, and thus etiologic, relations between these defects. Some of the combinations might have been predicted, since they are components of the tetralogy complex, others may be a surprise since they would not have been thought of as minor forms of this defect. A similar analysis of a large number of families of various European sources came to a similar conclusion, viz. that anatomically different malformations may be related etiologically (Corone et al. 1983).

Several decades of further observation and analysis hardly changed such perceptions. An extensive examination of familial risk for individual heart defects was made as part of the ongoing Baltimore study (Boughman et al. 1987). The defects were classified anatomically and mechanistically, with the latter designation divided into five named categories, emphasized in examining for occurrence of a defect in a relative of a proband.

Of the first category, defects of cell migration (including transposition of the great vessels, tetralogy of Fallot, etc.), none occurred in parents or sibs. Of the second, flow lesions (hypoplastic left heart, coarctation of the aorta, etc.), the frequency was increased in sibs, more than in either parent, and varied by particular defect, ranging from 3.2 % for atrial septal defect to 13.5 % for hypoplastic left heart. In the categories involving cell death, extracellular matrix, targeted growth (Ebstein anomaly, etc.) again no parent or previous sibling was affected. Small number of family members was again the bane of this study, and made any conclusion or prediction dangerous.

The application of the mechanistic approach to classification, based on the logical sounding assumption that a limited number of pathogenetic pathways is responsible for the many outcomes, does not seem to have allowed any more profound analysis or pointed family counseling than an uncomplicated anatomical one. Almost predictably what was urged were “further family studies.”

The latest such report to come to my attention concerned a family study in Northern Ireland (Hanna et al. 1994). It was based on infants identified in 1974–8 by multiple sources as having heart defects, in 88 % of whom the diagnosis was made by 1 year of age. Excluding patients with syndromes known to be associated with heart defects, with undescribed chromosomal abnormalities (totaling another 4.9 %), and with affected parents, the frequency of heart defects in full sibs of the remaining probands was 2.6 % and in parents 2.8 %. There was defect concordance in eight of the eleven affected parent-offspring instances. Thus again simple Mendelian inheritance was disqualified as being the basis of the recurrence of these defects.

The family studies outlined above showed that simple hereditary factors–the ordinary genetic principles of the Mendelian type–cannot satisfactorily explain the causes of most heart defects. All together such factors may be responsible for only a small proportion of the entire frequency of cardiovascular malformations. An early guess put this fraction at perhaps 10 % or less (Nora and Nora 1978). The large fraction remaining is widely believed to be caused by the interaction of threshold characters whose expression is facilitated by environmental agencies, the multifactorial or multigenic theory (Nora 1968).

## MULTIFACTORIAL HEREDITY

The importance of the role of quasi-inheritance for heart defects, and in fact for congenital malformations in general, warrants full discussion of what it's all about.

In the beginning was Haldane (1946), who said that "the interaction of nature and nurture is one of the central problems of genetics," and positing variations in both, he noted four broad types of interactions, the ideal to be the "elimination of environments unfavourable to all genotypes, and of genotypes which are inferior in all environments." Difficult of achievement even in agriculture, impossible in people.

Just a few years later Penrose (1951), observing how the great reduction in infant death in the first half of the century had exposed "the hard core of less easily preventable deaths," called attention to their basis, "interactions between mother and fœtus of both hereditary and environmental origin." And thus "difficult to attribute to unique causes." It may safely be said that such interactions underlie the great majority of teratological disorders.

Ideas of this sort had emerged from and become concrete through teratological experimentation, their origins described in a recent history (Kalter 2003, pp 164–5) and their power to explain developmental phenomena made explicit by one of its founders (Fraser 1976). This episode in the story of multifactorial inheritance warrants telling.

During the years that saw the theories of multifactorial inheritance enunciated, teratological experiments had been proceeding which turned out to exemplify them. These had shown that congenital malformations could be caused by a variety of single discrete enviromental agents (Kalter and Warkany 1959), that genetic factors could modify outcome (Kalter 1954), and that fetal physiological forces were part of the developmental picture (Walker and Fraser 1956, 1957). From these studies a wide concept of multifactorial heredity, and especially the role of developmental thresholds, was elaborated (Fraser 1976).

These ideas, it is to be remembered, were based on interactions occurring in experimental animals, between maternal and fetal genes and specific environmental agents. The theory had also been more broadly formulated with regard to developmental situations in human beings in which the interactions were between genes and unidentified environmental elements, e.g. with respect to orofacial clefts, neural tube defects, and other common congenital malformations (Carter 1969).

And it was with regard to such occasions and situations that several principles were laid down by which to recognize this hereditary pattern: the risk of recurrence increases with the number of affected relatives of probands; the malformation frequency rapidly diminishes with remoteness of relationship to the proband, the ratio depending on the frequency in the overall population; the proportion of affected relatives is influenced by the severity of the malformation and by the sex of the index patient–the last because patients of the more rarely affected sex tend to be more extreme deviants from the population mean, and thus the risk to their relatives is correspondingly greater (Curtis et al. 1961, Carter 1977). A classic example of the last provision is demonstrated by pyloric stenosis, in which children of female patients were affected far more often than children of male patients (Carter 1969).

Bringing the concept down to earth, Fraser (1980) wrote that it merely invokes a "simplifying assumption to reduce the complexity of real life to manageable terms," and thus was an expedient for "managing complexity and hopefully one day leading to deeper understanding and more precise genetic counseling."

CHAPTER 18

# EXTRINSIC CAUSES OF CARDIOVASCULAR MALFORMATIONS

Having more or less given the hereditary fraction of the equation its due, we move on now to environment, to see what part it may play in the matter.

Many environmental factors have been accused or suspected of causing congenital defects of the heart. It is another matter to prove it. They come in a variety of categories. Let me count the ways. Being au courant, one category could be given the euphemism maternal lifestyle, and include things like cigarette smoking, caffeine, cocaine, marijuana, alcohol, etc. Others are many, and a few will be considered below.

## LIFESTYLE

The first 'lifestyle' factor to be linked to heart and other defects was maternal cigarette smoking (Alberman and Goldstein 1971). But it had a short shelf life, and the supposed connection was soon clearly disproven when examined in depth (e.g. Yerushalmy 1973, Evans et al. 1979, Shiono et al. 1986b, Tikkanen and Heinonen 1991, McDonald et al. 1992, Wasserman et al. 1996, Williams et al. 2004). Drugs of abuse, to use another euphemism, such as cocaine and marijuana, also fall into this category. A number of studies examined the relation between maternal use of cocaine during pregnancy and certain heart defects, but limited number of subjects and wide statistical intervals made for risk uncertaintly (see Williams et al. 2004).

Another one of this category that has been claimed to be a teratogen is maternal consumption of alcoholic beverages, not so easily vanquished. The assertion at first was that it principally caused certain minor craniofacial asymmetries as well as questionable cardiac conditions. This is a big topic and deserves an in depth inspection.

## ALCOHOL CONSUMPTION DURING PREGNANCY

The last 40 years saw a torrent of articles in which maternal consumption of alcoholic beverages during pregnancy was held to be responsible for innumerable developmental abnormalities. The earliest few studies apparently struck a chord and

were followed by a deluge that attributed a set of conditions in children to maternal alcoholism, conditions that were labeled the fetal alcohol syndrome; consisting, in essence, of certain craniofacial characteristics, impaired prenatal growth, and cardiac anomalies (Jones et al. 1973). It is the last of these we are especially concerned with here.

The Jones article described in detail the findings in eight affected children of supposedly severely alcoholic women, aged from 11 weeks to 4 years, among whom were five with cardiac anomalies. These consisted of one child with a patent ductus arteriosus, another an atrial septal defect confirmed by catheterization, and the remaining three transient murmurs thought to represent closed ventricular septal defects.

It is impossible to judge the meaning of these observations without first describing their ascertainment, which was unusual to say the least. To wit, four of the children were "recognized as having a similar pattern of altered growth and morphogenesis." Two others were then discovered by the abnormal features that "identified" the first four; and the last two because their mothers were chronically alcoholic. Thus the backward leap was made that the first six were also the products of an alcoholic milieu because they resembled the last two, who had this history. In other words, the mothers of only two of the eight subjects were known to be alcoholics, and for the others such was assumed.

Other reports of a retrospective nature, i.e. studies of children of a wide range of ages of mothers said to be alcoholic soon appeared. In one of these, children were found to have heart defects, mostly ventricular septal defects, many small, few requiring surgery (Sandor and Smith 1981). As was true of similar reports, contemporary and later, it lacked a control group. How the patients were ascertained was not noted, particularly important here because the majority were American Indian, a group then having many social problems, clearly relevant to a study of children of problem milieux.

These findings should be contrasted with those of a retrospective case-control study of Northern Plains American Indian children with fetal alcohol syndrome identified in 1981–93 (Kvigne et al. 2004). Mentioned among the symptoms were numerous signs of the condition, such as facial dysmorphology, growth deficiency, etc., but no congenital malformations.

A clinical report from a cardiology department in Germany was concerned with children said to have the fetal alcohol syndrome, not otherwise described, whose mothers drank excessive amounts of alcohol during pregnancy (Löser and Majewski 1977). Many, almost all premature or underweight, had heart defects, mostly atrial septal defects. An updated report of later findings noted heart defects in 29% of children with the fetal alcohol syndrome, three-quarters ventricular and atrial septal defects, most being offspring of severely alcoholic women (Löser et al. 1992). Again there was no control.

Many infants with severe fetal alcohol syndrome seen in 1980–85 in a hospital in Chile had heart defects, including ventricular septal defect and tetralogy of Fallot (Mena et al. 1986). Direct evidence of maternal alcohol consumption was not always available, but some women were said to be alcoholic.

A population-based study, which included controls, found conotruncal heart defects, i.e. anomalies of aorticopulmonary septation, in 1.2/1000 neonates plus fetuses born in some districts of California in 1987–8 (Carmichael et al. 2003b). The mothers were interviewed by telephone, about three and a half years after the date of delivery, and asked about type and amount of alcohol consumed four and half years earlier. Case mothers who drank during the periconceptional period, relative to nondrinking mothers, had a slightly increased risk of having infants with these heart defects, which somewhat increased with volume of alcohol consumption. As the authors noted "most of the risk estimates were imprecise, and chance could not be ruled out as an explanation for the observed findings." What was not commented on was the possibility of faulty maternal recall years after a lengthy interval.

The relation between amount of alcohol consumed during pregnancy and congenital heart and other congenital anomalies was examined in a Spanish multihospital-based case-control study (Martínez-Frías et al. 2004). The amount consumed, sporadically or daily, was divided into five levels; controls were infants whose mothers denied drinking during pregnancy. Only consumption at the highest level, that of more than 92 g/d of absolute alcohol, was statistically significantly related to cardiovascular defect, the 8/1000 frequency being many times greater than that of the controls, though within the range often found by others. The defects were not named and the inclusion among them of vascular anomalies made it impossible to judge their acceptability.

A case-control surveillance program based in Boston examined the association between alcohol consumption and malformations of different developmental derivations (Werler et al. 1991). This ambitious scheme found but a single associated defect to be increased, cleft lip with or without cleft palate, in children of mothers drinking heavily and frequently (i.e. >5 drinks/d). But even this finding was based on rather questionable evidence.

A study was made of young and adolescent children of alcoholic women in the Helsinki area (Autti-Rämö et al. 2006). Heavy maternal alcohol consumption was established retrospectively, i.e. years later, by review of various records. The subjects, aged 8 to 20 years, had signs equated with the fetal alcohol syndrome or one of its variants, principally various minor dysmorphic facial features. Also "14 patients . . . reported congenital heart defects . . ." No professional verification of these defects was mentioned. What is to be made of this statement is beyond knowing. All the subjects had resided in multiple foster placements, virtually all were enrolled in special education programs. Therefore the report is clearly unacceptable.

## SUMMARY

Examination of the teratogenic effects of maternal alcoholism came to a dead halt, it seems, by the final decade of the last century. The vast majority of articles of the past 10–15 years (I write this toward the end of 2006) that dealt with its consequences, instead, were almost entirely concerned with older children who possessed the "essential diagnostic criteria of the fetal alcohol syndrome . . ." (Elliott

and Bower 2004), viz. facial dysmorphology, neurodevelopmental deficits, aberrant sociobehavior, anthropometric distortion, etc., and rarely if ever congenital malformations (e.g., Harris and Bucens 2003, Viljoen et al. 2005, Fiorentino et al. 2006, May et al. 2006).

Why this is so is hard to say. Or is it? Claims of alcohol causing almost every known congenital malformation have failed to be proven or confirmed. What is left are the soft signs associated with maternal alcoholism, with the fact of this alcoholism usually taken for granted. It profiteth not to labor the point. An excrutiatingly detailed exposition of the entire question is found in Kalter (2003, pp 237–56). [A ludicrous footnote: French wine makers are being sued for not labeling their product as harmful (Burgermeister 2004).]

It is safe to say, in conclusion, that consumption of alcohol during pregnancy has not been proven to cause major congenital malformations of the cardiovascular system or of any other part of the body.

## BENDECTIN

Numerous agents have been accused of causing heart defects, the majority with no solid evidence. These include the drug called Bendectin in the US, prescribed to combat nausea and vomiting of pregnancy, accused of causing a host of fetal abnormalities, including heart defects, that were never proven. A case-control study in fact found that it apparently protected against the occurrence of heart defects (Boneva et al. 1999). The downfall of what had been a useful pharmaceutical product cannot be given the space it deserves here; its sorry history is found in my inestimable compendium, Teratology in the Twentieth Century (Kalter 2003, pp 175–7).

## FEMALE SEX HORMONES

Certain female sex hormones, said to be associated with a number of congenital malformations, largely ceased being used after the US Food and Drug Administration warned of their potential harmfulness in 1977. These classes of hormones, the progestins and progestogen-estrogen combinations, had been taken during pregnancy for several purposes, including contraception, pregnancy testing, and supportive therapy for threatened or recurrent abortion.

Their use continued for other purposes however, with frequent reports of their association with congenital malformations, particularly of two classes, genital and nongenital. About the former there was little disagreement, progestins administered in early pregnancy could masculinize female fetuses.

With regard to nongenital defects the story was different. A heterogeneous assortment of malformations was said to be associated with their use, among them cardiovascular malformations. The latter suggestion was examined in a sizable study in Boston, based on data from the Collaborative Study, described above (Heinonen et al. 1977). Boiled down to the essentials, the overall frequency of heart defects in

children whose mothers received female hormones in the 1st trimester of pregnancy was 18.2/1000, while the frequency in children whose mothers did not receive the hormones was 7.8/1000, a statistically significant difference. Agreeing with previous reports, this study supported the possibility that these drugs may disturb normal development of the heart.

However, pay attention and follow this: a paper quite soon appeared which disputing this conclusion pointed out some serious flaws in the methodology of the analysis, which negated it (Wiseman and Dodds-Smith 1984). This in turn was challenged by an article, which when first published was said to contain errors and was then republished in corrected form (Hook 1994). Reevaluation of the reanalysis found that the contention still remained, and in fact was said to be strengthened, that there was a positive association between induction of defects and sex hormones. This rebuttal was then didactically responded to by invoking facts known in 1994 that were not in 1977, which would bear upon the original study's design, and finally by citing numerous review articles, in none of which it was concluded sex hormones caused nongenital malformations (Brent 1994). And that is where a decade or more later the matter rests.

## LITHIUM

The lithium story, also long and complicated, told in detail elsewhere (Kalter 2003, pp 222–4), can be summarized thusly for our purpose here. The accusation against it, that it caused a very specific heart defect, the ordinarily rather rare Ebstein's anomaly, in fetuses of women treated with the drug early in pregnancies for bipolar disease, was eventually conditionally retracted. But not until after much examination and reexamination of reports of its occurrence (Warkany 1988). Even today the evidence is still considered unclear as to whether lithium can cause this heart defect or not (Giles and Bannigan 2006), but the weight of the scales is against it.

## ANTIEPILEPTIC DRUGS

The story of the rational efforts to control epileptic seizures, begun in the 19th century, and the suspicion many decades later that antiepileptic drugs then in use were teratogenic, and the efforts to formulate others that it is hoped would be less so, is long and tortuous (Kalter 2003, pp 215–24).

Many studies found that the overall frequency of congenital malformations in offspring exposed to antiepileptic drugs in the 1st trimester, though it varied from study to study, was about twice that in the general population. The variation, among other things, stemmed from different proportions of mono- and polytherapeutic treatment, the latter far more teratogenic than the former, and differences in the abnormalities included in the count, which although usually not made explicit consisted of both major and minor defects. Reports listing abnormalities individually made it possible to verify this supposition (e.g. Kaneko et al. 1988,

Canger et al. 1999, Kini et al. 2006). Especially prominent among the named defects were cardiovascular malformations.

This was made evident very early when 18 infants, one with Down syndrome, exposed during pregnancy in 1963–75 to several antiepileptic drugs had various heart defects, in a total of about 3000 new pediatric patients with heart defects seen at a university hospital (Anderson 1976). Thus the frequency of heart defects in children exposed prenatally to such drugs was 6/1000, but only 1.3/1000 monotherapeutically, not out of the background range. This is the only such study I am aware of, i.e. of the incidence of antiepileptic associated-heart defects in a population of children with heart defects. Most other studies were of a conventional nature.

Epileptic women in several hospitals in Japan in 1978–84 received many different antiepileptic drugs during the 1st trimester of pregnancy, only 18% a single drug (Kaneko et al. 1988). Seen in their infants were 4.6% congenital malformations and 17/1000 infants with heart defects, amounting to two ventricular septal defects and one patent ductus arteriosus.

Epileptic women receiving various antiepileptic drugs during early pregnancy were followed prospectively in 1977–91 in a Milan hospital (Canger et al. 1999). The 89% of infants exposed to single drugs had a frequency of major congenital malformations of 4.8%, and a miscellany of heart defects in 10/1000. Those exposed to two or more drugs had frequencies similar to those exposed to one drug, which is unusual since polytherapy has been associated with higher rates than monotherapy.

One report was based on a survey of studies of fetal exposure to the antiepileptic drug carbamazepine (Matalon et al. 2001). Many studies were identified of women given antiepileptic drugs during pregnancy, which yielded information about the teratogenic effects of this drug alone or in combination with other such drugs. All told, congenital malformations occurred in 6.8% of the children; using stricter criteria, the frequency became 5.3%. In control children and those of untreated epileptic women the frequencies were 2.3% and 2.8% respectively. Those from monotherapy and polytherapy treatment respectively were 5.5% and 11.6%, apparently using the original criteria. As for heart defects, which were the most frequent type of malformation found, mono- and polytherapy differed little, both causing defects of about 1.8%. Specific comparison with control children regarding heart defects could not be made.

A prospective study of births to epileptic women receiving several antiepileptic drugs in early pregnancy in 1978–91 in Japan, Italy, and Canada found 7.8% congenital malformations after monotherapeutic exposure and 10.6% after polytherapy (Kaneko et al. 1999). The only heart defect frequency given was for the entire sample, 16/1000, but neither the composition of the defects nor how many occurred after single drug treatment was mentioned.

Neonates born in 1972–94 in numerous hospitals in the Netherlands were exposed early in pregnancy to numerous antiepileptic drugs, 64% to single drugs (Samrén et al. 1999). The frequency of malformations was somewhat less in the latter, 3.3%, than in the multiply treated, 4.8%; but that of heart defects, named and unnamed, 6/1000, was reported only for the whole group.

In births in 1980–98 in Helsinki, 80% of exposures were monotherapeutic, giving 3.1% malformations, not very different from the 3.8% in the whole group (Kaaja et al. 2003). The frequency of unspecified heart defects in the whole group was 8/1000. An interesing parenthetical remark was made, that "in families with an affected offspring in the current series, no prior children with malformations were reported."

In a limited hospital-based study in Boston in a 32-month period only one offspring of epileptic women given clonazepam alone was malformed, the one defect consisting of tetralogy of Fallot, for a frequency of 33/1000, one not to be taken very seriously (Lin et al. 2004).

A retrospective study in 1989–99 of children of ages 6 months to 16 years born in Manchester and Liverpool found a frequency of major malformations of 2.1% in those exposed prenatally to single drugs, 2.9% in all exposures, and 2.0% in the nonexposed. That of heart defects, very few in number, was 14/1000 exposed children, and 10/1000 nonexposed ones (Kini et al. 2006), an apparently high one, provoking suspicion of the reporting system as a whole.

In the years most recent to this writing reports of population-based studies listing the malformations, including those of the heart, in infants exposed early in pregnancy, usually to a wide variety of these drugs have grown in number.

Prospective data from five European centers collected in 1971–90 were pooled to examine the teratologic risks of taking antiepileptic drugs during pregnancy, almost 80% of single drugs (Samrén et al. 1997). The frequency of malformations, major and minor, after monotherapy was 7.5% and after polytherapy 10.7%; but it appears that most of the defects were of a minor nature. Unnamed heart defect frequencies were hardly different in both regimens, 11.2 vs 11.7/1000.

A population-based study was made in Iceland of all resident epileptic women pregnant in 1972–90 (Olafsson et al. 1998). The frequency of major congenital malformations in neonates exposed prenatally to antiepileptic medication was 5.4%, compared with the 2.2% population baseline. In the 53% of infants exposed to a single drug 2.5% were malformed, while in the polytherapy group it was 8.7%. Few heart defects were seen (2 mild ventricular septal defects, 1 persistent ductus arteriosus), for an overall frequency of 14/1000.

An Australia-wide registry of self-enrolled pregnant epileptic women in 1999–2002 enabled a comparison of the malformation frequency in offspring exposed to various antiepileptic drugs, finding that valproate caused more major malformations than all others, 12.6% vs 1.8% (Vajda et al. 2004). Heart defects of various sorts occurred in 13/1000.

A population-based study was made in Sweden in 1995–2001 of the outcome of pregnancies of epileptic women (Wide et al. 2004). The most widely taken drugs, carbamazepine and valproic acid, 89% as monotherapy, together caused 2.8% major congenital malformations, i.e. similar to the background level, with the risk from the latter drug seeming higher than from the former. The rate of undescribed heart defects was 14/1000.

An international registry was used to assess the outcome of pregnancies in 1992–2004 of epileptic women taking lamotrigine alone or combined with valproate or non-valproate drugs (Cunningham et al. 2005). The frequency of congenital malformations after exposure to lamotrigine alone or combined with non-valproate was within the background level; only when combined with valproate was the risk elevated. The frequency of various heart defects also was apparently increased only when lamotrigine was combined with valproate, being 7/1000 after monotherapy and 21/1000 after polytherapy including valproate.

A USA and Canada registry was constituted of epileptic women prospectively self-enrolling in 1997–2002 who had taken a small number of antiepileptic drugs monotherapeutically (Holmes et al. 2004). The neonatal infants of the relatively small number taking phenobarbital had a frequency of major congenital malformations of 6.5%, and of 2.9% in those taking any one of three other antiepileptic drugs. Heart defect occurrence, 52/1000, consisting of four different defects in four offspring, was listed for the small number exposed to phenobarbital only.

Epileptic women prospectively self-enrolled in a North American registry in 1997–2003 had infants with 6.0% major congenital malformations exposed to valproate monotherapy, and 3.0% to various other antiepileptic drugs taken singly; with various heart defects occurring in 34/1000 infants in the valproate group (Wyszynski et al. 2005).

A Finland-wide study of infants born in 1993–2000 exposed during pregnancy to antiepileptic drugs had a frequency of congenital malformations noted in the 1st year of life of 5.4% vs 2.8% in nonepileptic women; and heart defects of 19/1000 vs 12/1000 respectively (the latter suspiciously high), the excess due predominantly to bulbus cordis and septal closure anomalies (Artama et al. 2005). The medications were not specified, nor was the proportion given singly or with another such drug concurrently or otherwise. Thus how much of the excess frequency may have been due to polytherapy, known to be responsible for greater teratogenicity, could not be determined. This is true also of other studies discussed here not giving such details.

In a retrospective population-based study of pregnancies of epileptic women giving birth in Beersheba, Israel in 1988–2002 the frequency of infants with congenital malformations was 7.7% and in those of nonepileptic women 3.8% (Katz et al. 2006). Perinatal mortality was moderately increased, 1.8% vs 1.3%. Information regarding malformation and medication type and proportion single drug-treated was not mentioned.

Pregnancies of epileptic women reported to a UK registry by medical persons or by the epileptic women themselves, taking various antiepileptic drugs singly or in combination in 1996–2005 were described in detail (Morrow et al. 2006). The frequency of infants with major congenital malformations after polytherapy was 6.0% and after monotherapy 3.7%, the latter hardly different than the 3.5% in infants of epileptic women taking no antiepileptic drugs. Only valproate caused a significantly higher frequency of malformations, 6.2%, than occurred in unmedicated pregnancies. As for heart defects, not named, the three most frequently used drugs,

carbamazepine, valproate, and lamatrigine, were all associated with frequencies of about 6–7/1000, i.e. apparently of the order in the background.

## CRITIQUE

Almost four decades of study of the teratogenic risks run by the offspring of treated and untreated epileptic women yielded great understanding of the problem. But along the way much misapprehension and premature pronouncements have had to be corrected. As to teratogenic risk posed by the various antiepileptic medications now generally in use, phenytoin, phenobarbital, valproic acid, and carbamazepine, it appears that only valproic acid is culpable, and that its most distinguishing effect is the neural tube defect spina bifida; but even for that there is some doubt which only the future may resolve.

It had usually been found that antiepileptic medication carries a twofold risk of causing major malformations, but the like facts regarding heart defects are not yet conclusive. What is this opinion based on? Some caveats are to be considered. The findings are weak and tentative, since even in the largest studies only a relatively small proportion of the epileptic women in the population were ascertained and relatively few of their infants had heart defects. To be acceptable the account must be based on defects in infants exposed to single drugs; and this information is scarce. Many of the larger studies described were founded on women who were self-enrolled, a method that carries the danger, as the authors of one of these studies noted, that "such individuals do not represent the entire population of pregnant women taking antiepileptic drugs . . ." (Wyszynski et al. 2005). The studies were mostly made with the older antiepileptic drugs, well established as being teratogenic; newer ones that carry promise of being safer have not yet been used extensively enough to confirm their promise.

## EPILEPSY INCIDENCE

Let us now try to summarize what these findings tell us about how often heart defects are caused by antiepileptic drugs, and learn what meaning it may have. To calculate the dimensions of the matter, let us first calculate how many pregnancies occur to epileptic women yearly. Epilepsy is one of the commonest chronic diseases of humankind. The Centers for Disease Control reported that in the US it affects 5.6 per 1000 women aged 15 to 45 years of age (Anon. 1994c), a figure that hasn't changed in many years (Niswander and Gordon 1972). In Boston in recent years it was 5.8 per 1000 (Lin et al. 2004), and this is true elsewhere as well; e.g. in an area in Israel it affected 5.6 per 1000 pregnancies (Katz et al. 2006). Thus, based on current estimates of about 4.1 million annual US births (Martin et al. 2005), about 22,900 epileptic women give birth annually.

It is a safe bet that in the US nowadays practically all epileptic women receive antiepileptic treatment during pregnancy. The consensus appears to be that the illness is not teratogenic; thus it is the drugs, or some of them, that are responsible

for causing congenital malformations. In the reports of pregnancies of epileptic women outlined just above heart defects of no particular constellation were most often found to occur at rates of about 16–17/1000, i.e. about four times the estimated background frequency of significant heart defects.

Therefore in 4.1 million US births there would be about 16,400 offspring with heart defects; while in the 23,000 pregnant women administered antiepileptic drugs the number of offspring with heart defects would be 391; i.e. 2.4% of all births with heart defects would have been those caused by antiepileptic drugs, a considerable number, but one that must be kept in perspective.

## PHENYLKETONURIA

Phenylketonuria is the only known human metabolic disorder that is teratogenic, and that alone merits the great attention it has received. It is an autosomal recessive trait consisting of inability to convert the essential amino acid phenylalanine to tyrosine due to deficiency of phenylalanine hydroxylase. Phenylalanine thus accumulates in blood and almost invariably leads to severe mental retardation. Not until 19 years after the biochemical basis of the condition was recognized (Følling 1934) was it discovered that a diet limiting intake of phenylalanine initiated early in infancy, i.e. before symptoms of the retardation are usually present, can prevent the mental deterioration. And a further 10 years had to elapse before this knowledge was applied, by screening of newborns with ferric chloride, to detect the infallible sign of the condition, the breakdown products of elevated phenylalanine in urine.

In the years before this therapy was devised the disease was so severe that pregnancy in phenylketonuric women was extraordinarily rare. The diet restored fertility, but the resulting pregnancies frequently had unfavorable outcomes, the nonphenylketonuric infants often being growth retarded and severely microcephalic, due to the fetotoxic effects of phenylalanine of maternal origin, but with no obvious congenital abnormalities. This soon changed when infants of such women were reported with microcephaly and multiple heart defects (Stevenson and Huntley 1967). The disease was thus a tragic example of a medical condition whose ‘cure’ had unforeseen harmful consequences.

The gravity of the maternal condition was affirmed by the great frequency of the abnormalities. A program conducted in 1984–95 enrolled pregnant women with phenylketonuria known to metabolic clinics and obstetric units in the US and later in Canada and Germany. Heart defects confirmed by postnatal echocardiography were found in 7.5% of newborns exposed prenatally to a blood phenylalanine level $\geq$900 $\mu$M when the pregnancy was not in metabolic control by the 8th week of gestation; normal is less than 120 (Rouse et al. 2001). The children had many types of heart defects, but only coarctation of the aorta and tetralogy of Fallot occurred in a significant excess (Levy et al. 2001). It must be remembered however that in toto only a relatively small percentage had malformed hearts.

A study in 1978–97 of all known women with phenylketonuria in the UK largely confirmed these findings (Lee et al. 2005). The usual array of harmful

outcomes, called a distinct syndrome, was found: facial dysmorphisms, microcephaly, intrauterine growth retardation, and congenital heart defects. The frequency of the last was 2.4% when the phenylalanine restricted diet was begun before conception, and 17% when begun afterward. The defects were not named.

## MEDICAL AND ETHICAL QUESTIONS

What began as a revolutionary medical advance, one that promised to correct a serious hereditary disease and to eliminate a major cause of mental retardation, instead led to creating many medical and ethical difficulties. How sizable a problem has followed? Phenlketonuria is one of the commonest inborn errors of metabolism. It is estimated, taking an intermediate among some calculations, that in the US it afflicts 1 in 15,000 births; hence in round numbers the annual number of girls with the disease born in the US, with about 4.1 million annual births, is 130, and the total number since 1966, the year widespread neonatal phenylketonuria testing was mandated, 5200.

Only a fraction of this number have been identified. One wonders, where are the others, and how representative are the comparatively few that have been found? It is clear that most women with the condition have not been seen in any collaborative study. Also left for the future to consider are the consequences of the newly won fertility of women with phenylketonuria. Has it increased the population load of microcephaly and cardiovascular malformations? Many questions regarding population dynamics and disease projections posed by this problem, and many citations not included here, are found and discussed in Kalter (2003, p 188).

## RUBELLA

Rubella, a human infectious disease, common and hardly likely not to have been of long standing, was discovered early in 1941 to be the cause of serious congenital malformations. The announcement of this momentous discovery was made by an Australian ophthalmologist, Norman McAlister Gregg, at the Royal Alexandra Hospital for Children in Sydney: "... an unusual number of cases of congenital cataract made their appearance ... what might almost be regarded as a mild epidemic" (Gregg 1941). Gregg soon deduced and maternal histories diligently probed by him confirmed that it was no coincidence that the pregnancies bearing the affected babies dated to a time of maximum intensity of an unusually severe epidemic of so-called German measles or rubella that had swept Australia during the difficult wartime conditions of 1940.

In addition to eye and other abnormalities there occurred congenital defects of the heart in "an extremely high percentage of the babies" (Swan et al. 1943). The "extremely high percentage" was 55%, over one-third without other apparent defects. Based on radiological evidence and autopsy examination, these consisted of widely patent ductus arteriosus with foramen ovale, combined with ventricular

septal defect. The important fact was determined that almost all the affected infants had been exposed to rubella in the first 3 months of pregnancy.

A summary of numerous Australian, English, and US publications in 1941–7, of defects in children of women contracting rubella during pregnancy found that heart defects were reported in 42% of 521 cases (Wesselhoeft 1947). This high level was disputed by Rutstein et al. (1952), whose literature search yielded specific heart lesions in only 17% of 442 reported cases, and Bell (1959), whose search was a bit more productive, finding almost 30%.

This skepticism about how often heart defects were caused by rubella, perhaps justified, since some were based on less credible retrospective observations, was on the whole challenged by later more precise findings. These dealt however with overall malformation frequency, e.g. 85% reported by Horstmann (1965), after the devastating 1964 rubella epidemic in the US.

Several efforts undertook to correlate frequency and timing. Bell (1959), in her review, found few heart defects later than week 9–12 infection, most associated with deafness. Campbell (1961), in an important review, found the highest overall risk after 1st-month infection, sometimes as great as 100%, but generally 30–70%, and lesser ones after later 1st-trimester infection, with heart malformations occurring especially after infection in the 5th–9th weeks.

Tabulated by type and combination the most frequent heart defect by far was persistent ductus arteriosus, at 58%, most frequently combined with ventricular septal defect, which it was commented on was unusual. Other types were far less common, e.g. ventricular septal defect, 18%, tetralogy of Fallot 7%, etc. All in all, the defect frequencies and combinations were "totally unlike anything that is found elswhere, and helps to justify the use of such a term as the 'rubella syndrome.' " Campbell, introducing a crucial topic, also considered the "proportion of cases of congenital heart disease due to maternal rubella," finding numerous computations put it between 1% to as high as 8%, he himself thought it unlikely to be more than 3–4%.

As noted above, early description of the congenital malformation risk was exaggerated by its retrospective nature. More reliable qualitative and quantitative depiction was enabled by prospective examination of children following an outbreak of rubella in England and Wales in 1978 (Miller et al. 1982). Children of women contracting symptomatic rubella were found to have been infected at all stages of pregnancy, but congenital abnormalities were only present in infants infected in the first 16 weeks of pregnancy, heart malformations and cataract in the first 10 weeks, etc. Also confirmed was the early finding that in neonates heart defects far exceeded ocular ones.

Rubella presents an example of the virtual disappearance of a cause of human teratogenicity. The isolation of the rubella virus in 1962, development of the vaccine that it permitted, the mass vaccination that followed licensure of the vaccine in 1969, all but wiped out the congenital rubella syndrome (Cochi et al. 1989), which however by the turn of the century had still not been fully accomplished (Reef et al. 2002).

An irony must be noted of the picture vis-à-vis rubella and phenylketonuria. Both are 'natural' afflictions, but while on the one hand the latter, we learn, is on the

verge of extinction, the former is an omnipresent and growing worry. What they have in common, we must be reminded, is that their present state of promise and threat both transpired through the agency of human action.

## DIABETES

Diabetes is an old disease, but only with the discovery of insulin early in the 20th century (Banting and Best 1923) did it become possible for diabetic individuals to reach sexual maturity and old age. The discovery also brought in its wake the harmful complications of the disease that emerge at older ages, as well as those associated with pregnancy, providing yet another example of a medical advance of great promise that gave rise to unimaginable health problems.

Although it was known years before, only in the 1960s did the realization became crystallized that with respect to pregnancy there are two forms of diabetes, one that occurs during pregnancy, called gestational diabetes, and the other that precedes pregnancy, which differ from each other in fundamental ways. It is the latter–type 1 or insulin-dependent diabetes mellitus of pregestational origin–that is the predominant subject here.

Unlike phenylketonuria, insulin-dependent diabetes is relatively common, with a prevalence of about 5 per 1000 persons. Pregnancies of diabetic women have been prone to various detrimental outcomes–increased perinatal mortality, increased spontaneous abortion, large babies, and congenital malformation. It is the last of these we are concerned with here, in particular those of the cardiovascular system.

Isolated instances of congenital malformations in children of diabetic women were reported soon after the introduction of insulin, but it was not until the 1960s that evidence was provided of an excess of congenital malformations in diabetic pregnancy (Mølsted-Pedersen et al. 1964). Children of diabetic mothers born in 1926–63 in a Copenhagen hospital had a frequency of 5.2% major congenital malformations. The abnormalities were not named, but from a list that was made available it was seen that some number of them were not of the sorts usually considered major and others could not have been caused by the diabetes (see details in Kalter 2000, pp 122–3), omitting which reduced the frequency to 4.7%. The heart defect types, not named in the paper, were listed elsewhere (Rowe et al. 1981, p 678), giving the frequency as 17.5/1000. A broad report by Pedersen (1977), amplifying these findings, noted that almost one-quarter of the heart defects were fatal.

A report from this source more than 20 years later brought the findings up to date (Mølsted-Pedersen and Pedersen 1985). The malformation frequency in 1926–78, which included the interval considered earlier, was fairly constant over that span, at 7.6% (the malformations were not named; but no doubt included minor defects). In 1979–83, however, there was a substantial decrease, to 2.8%, for which the authors could offer no explanation. Whether this reduction was due to a difference in the array of defects could not be judged, since as noted the defects were not named; nor whether it could be attributed to reduced perinatal mortality, which undoubtedy occurred, since the number of deaths and facts regarding them were

not noted. The importance of mortality for dealing with diabetes teratogenicity will be discussed below.

Let us continue with findings of heart and other malformations. A compilation of worldwide reports found a 1% frequency in children of diabetic women, which undoubtedly included minor as well as major anomalies, approximately five times that found in controls (Kučera 1971). The sources lacked information about diabetes type, etc.; nor were perinatal mortality details mentioned.

A fairly large number of children of diabetic mothers born in 1962–8 in a Boston hospital followed up to age 7 years had a 4.0% heart defect frequency, i.e. about five times that in the overall population (Rowland et al. 1973). The defects consisted mostly of transposition of the great arteries and ventricular septal defects, as well as various others. At what ages they were diagnosed was not stated. Over four-fifths of the children with defects were stillbirths and neonatal and infant deaths; giving a frequency of 0.7% in the survivors, i.e. well within the background range. The controls were infants of diabetic women that lacked heart defects, a strange selection that could be of no comparison value.

A small number of children of diabetic mothers were seen at a Chicago hospital in 1977–81 (Simpson et al. 1983). Heart defects were reported in 3.3%, but the age at which the defects were detected was not noted (fewer than half were examined at birth; mortality was not mentioned). The defects consisted of a nonspecific assortment, ventricular septal defect, atrioventricular canal, patent ductus arteriosus, and tetralogy of Fallot. The small unmatched control sample was of no use for comparative purposes. The unclear manner of detecting the defects, described as "blind," was a source of uncertainty.

A large supposedly unselected sample of pregnant diabetic women was investigated by questionnaire survey in the UK in 1979–80 (Lowy et al. 1986). In babies of pregestational diabetic women the perinatal mortality rate was 5.6%, which was almost four time greater than in all UK babies in that period. Major congenital malformations were present in almost one-third of the deaths, as usual more in neonatal deaths than stillbirths. A further 19% died neonatally but without malformations. Prenatal death was not mentioned. Major malformations occurred in 4.3% of all babies, heart defects in 19.4/1000; as near as can be determined almost half of them were perinatal deaths, mostly multiply defective. The defects were mostly atrial and ventricular septal defects and patent ductus arteriosus. It could be calculated that the frequency of all major malformations in deaths was about 36% and in survivors 2.8%.

A broad study in Baltimore and its area identified a sizable number of infants with heart defects born in 1981–7 (Ferencz et al. 1990b). Of them 1.5% had mothers with overt diabetes, versus 0.5% in controls; only four of many defects were significantly related to the maternal condition, double outlet right ventricle, truncus arteriosus, tetralogy of Fallot, and ventricular septal defect. Also found was an even larger frequency of specific heart defects, 4.2%, in children of gestationally diabetic women, contradicting a literature survey clearly indicating that this form of diabetes is not teratogenic (Kalter 1998). The latter finding may thus have been

an example of overzealous examination, also reflecting perhaps on the principal finding. Mortality was not mentioned.

It is pertinent that a similar study failed to find a difference in the frequency of diabetes in the relatives of children with and without congenital heart disease (Fraser 1960).

A collaborative multi-hospital study of births in 1976–92 in Spain examined the frequency of malformations detected at birth (Martínez-Frías 1994). Undescribed and unnamed heart defects, "major and/or minor," occurred in 21.0% of infants of diabetic mothers and 7.5% of those of nondiabetic mothers. The size of the latter indicates a sizable admixture of less serious defects. The authors failed to mention the findings in mortalities, precluding analysis of the findings.

Outcomes in offspring of unselected women with preexisting insulin-dependent diabetes, in a study in 1990–4 in an area of northwest England, were learned of through maternity units and associated medical services providing care (Casson et al. 1997). During the period surveyed 9.4% of live births of such women were congenitally malformed, and 7.8% in those surviving to 1 year; thus 86% of neonatal and infant deaths were malformed. The most common defects, whose types were not specified, nor whether seen in deaths or survivors, were heart defects, at 39/1000. Nor were other malformations listed, but since hypospadias was mentioned as being common, it is not unlikely that minor ones were included. The frequency of malformations in stillbirths and infant deaths was 50%, while in survivors it was 7.4%. Even at this late date the rate of stillbirth and perinatal mortality significantly exceeded that in the general population.

Congenital malformations in infants of diabetic women born in 1987–97 were recorded by a national registry in Sweden (Åberg et al. 2001). Specified and unspecified heart defects occurred in 3.4% of infants of women with preexisting diabetes and 1.3% of those with gestational diabetes. One should again be reminded that a wide review found no increased malformation frequency in children of women with gestational diabetes (Kalter 1998). Mortality once again was not mentioned.

As in previous reports of the Baltimore-Washington study of children with heart defects, a later one concerned such defects diagnosed up to 1 year of age in children born in 1981–9 of diabetic women (Loffredo et al. 2001b). What was analyzed here was not the frequency of malformations in offspring of diabetic women but the frequency of diabetes in mothers of defective children. This was found to 2.4% compared with 0.5% in randomly selected controls. A large proportion of the case children, however, had cardiomyopathy, not usually considered a malformation. The rate of infant mortality in cases was more than twice that in controls, but the severity of the abnormalities in the former apparently was not greater than in the latter. The answer may instead be that the defects were more often multiple.

The outcome of pregnancy of women with pregestational diabetes in 1991–2000 at a hospital in Dallas, Texas was ascertained from discharge records (Sheffield et al. 2003). The overall malformation frequency was 6.1%, that of single organ systems,

2.9%. There was indirect evidence that minor defects were included in this account. The frequency of heart defects, which were unspecified, was 12.2/1000; while in nondiabetic pregnancy it was very low, 1.4/1000. Stillbirths were mentioned, but the malformations that may have occurred in them was not. A somewhat low pregestational diabetes prevalence (2.8/1000) occurred in the sample surveyed. Whether this means that some selection was practiced is unclear. The study also included offspring of a subset of gestationally diabetic women, who were said to have a malformation frequency of 4.8%, rather high, but with a heart defect frequecy in the expected range, 4.3/1000.

The subjects of a study in a northern health region in England were live births in 1995–2000 to women with preexisting diabetes (Wren et al. 2003). In this period the frequency of heart defects was 7.4/1000 in births to nondiabetic women and 36.1/1000 in those of diabetic ones; over a quarter of the last consisting of ventricular septal defects, plus an apparently larger proportion of transposition of the great arteries, tricuspid atresia, and truncus arteriosus than expected.

Only incidentally did the authors note that more than one-fifth of all the pregnancies of diabetic women during this period did not result in a live birth, and thus that the report omitted this considerable fraction of diabetic pregnancies. Also unmentioned were postnatal deaths, which it cannot be doubted occurred, and in all probability not in an insignificant amount, as the next cited item will show. Thus, as discussed below, an analysis must be considered incomplete and unsatisfactory that omits consideration of findings in mortalities, and its conclusions therefore held to be tentative.

A study conducted in France of all women with type 1 and type 2 diabetes delivering in a large number of centers in 2000–1 found a malformation frequency of 4.5% and 3.4% in the infants of these two groups respectively (Diabetes and Pregnancy Group, France 2003). A number of comments can be made about this report. The malformations were not listed or described, hence doubt may be entertained that they were all major defects. Almost half of the malformed offspring were perinatal deaths, which introduces a consideration discussed below. The characteristics of individuals with types 1 and 2 diabetes are usually quite different from each other, a matter not mentioned in this article, differences of sorts that make it difficult to accept that the latter has teratogenic consequences.

Selected women with type 1 diabetes attending antenatal clinics in the Netherlands gave birth in 1999–2000 to infants 5.6% of whom were reported to have major congenital malformations as well as a number of minor defects (Evers et al. 2005). An unstated number of chromosomal abnormalities were included as malformations (though diabetes can hardly be charged with causing such abnormalties). Some abnormalities were named, but details were not given; others affected perinatal deaths.

A population-based study was made of perinatal mortality and congenital malformations in offspring of type 1 and type 2 diabetic women delivering in England, Wales, and Northern Ireland from early 2002 to early 2003 (Macintosh et al. 2006). A considerable number of offspring died before the 1st month, 8.0% in type 1 and 8.5% in type 2, an improvement over former years, but still appreciable. Heart

defects occurred in 19.3/1000 in diabetes type 1 births and 13.8/1000 in diabetes type 2; but data for mortalities and survivors were not given separately. An intimation of this matter was noted, but only for all malformations: 20% in perinatal deaths and 2.4% in survivors at 28 days.

There are fundamental differences between these two forms of diabetes, which were not mentioned. In the study under discussion both types were pregestational, which in itself is unusual since type 2 ordinarily appears relatively late in life, often associated with obesity. Type 1 on the other hand is of juvenile or early adult onset. To a small extent this difference was reflected in this study, the onset time being 9–23 years in type 1 and 25–34 years in type 2, with no overlap. Another fact, strangely not mentioned, is that type 1 is insulin dependent and type 2 usually not so. Socioeconomic factors, as was found in this study, are important considerations for type 2, not for type 1. Such matters in themselves are relevant for malformation inquiry; they were not considered here in this light, especially the significant risk factor of obesity.

A report of specific congenital malformations in births in Hungary in 1980–96, based on a population-based, nation-wide registry, noted a frequency of heart defects up to 1 year of age of 4.5/1000 births in offspring of women with pregestational, insulin-dependent diabetes, which is approxiately the background level (Nielsen et al. 2005).

The extraordinarily high heart defect frequency of 15% detected in 2000–1 in neonates of diabetic women in a recent report from Saudi Arabia was explained as mostly due to early echocardiographic identification of minor forms of some conditions, not otherwise detectable, as well perhaps to the high consanguinity rate in Saudi communities (Abu-Sulaiman and Subaih 2004).

This section is concluded with a brief description of the findings of a prenatal study of insulin-dependent diabetic women (Albert et al. 1996). All women attending a diabetes in pregnancy program at the university hospital in Columbus, Ohio in 1987–93 were sonogramed at about 18 weeks of gestation. Ten percent of their neonates were found to have congenital malformations, about half cardiac and half various noncardiac malformations, almost three-quarters diagnosed prenatally. The defects were not all specified and hence their alleged major status could not be verified. Some of those that were named were not or may not have been major malformations or malformations at all. The one Down syndrome had no defects noted ultrasonographically. The neonatal mortality rate, 21%, of defective offspring was noted, but not that of the others. Data given regarding amniocentesis roused the suspicion whether all the women were unselected. Finally, it appears that the heart defect frequency found in this study, 52/1000, was in the range found prenatally in nondiabetic pregnancies.

## MORTALITY AND MALFORMATION IN DIABETIC PREGNANCY

What has seldom been taken into consideration in the analysis of congenital malformation and diabetic pregnancy, is the factor of offspring death, of significance because of a pair of key facts. First, over the course of the 20th century there was

a great decrease in perinatal mortality, in diabetic as in all pregnancy, falling in the latter from about 30–40% in the 1920s and '30s to as low as 3% at the end of the century. Keeping this in mind, the significance of the second fact, the inverse relation of rate of perinatal mortality and frequency of congenital malformation, becomes clear. By the 1980s in offspring dying in the 1st week of life the malformation frequency was over 30% (Kalter 1990, 1991), while in newborns remarkably it remained at about 3% (Warkany and Kalter 1961, Kalter and Warkany 1983).

Because of this difference between mortalities and survivors, valid analysis requires that the malformation frequency in them be considered separately. Performing this task with data collected from many sources (Kalter 2000, pp 102–9, 231–4) it was found, first, that the malformation frequency in perinatal mortalities of diabetic women was not significantly different than in those of nondiabetic women; and second, that the malformation frequency in surviving offspring of diabetic women was approximately the same as that in the general population.

Consequently the general finding that there is an increased frequency of malformations in diabetic pregnancy is due to the large perinatal and infant mortality in them; and it is to be expected that as this mortality rate decreases, the malformation rate will concomitantly decrease, and in time attain a level similar to the backgound one.

## PRENATAL DIAGNOSIS

Several studies from the late 1980s to the time of this writing were made to detect and diagnose cardiovascular malformations prenatally in fetuses of insulin dependent diabetic women (See Kalter 2000, pp 175–6 for citations to most of these studies). Over fifteen hundred fetuses were examined and heart defects diagnosed in 2–4%, and omission of questionable conditions reduced the frequency to about half. It is to be noted that not all the defects were successfuly detected prenatally, and not all were considered structural or "critical" (i.e. probably requiring surgical or medical intervention). The interesting fact mentioned in one study was that none of the mothers with defective previous offspring had recurrences (Meyer-Wittkopf et al. 1996). And finally, none of the mean glycemic levels, measured in three studies, was statistically significantly greater in women with abnormal fetuses than in the others.

## GESTATIONAL DIABETES

A brief mention should made of gestational diabetes, a condition of much confusion over the years. To begin with, some facts. Gestational diabetes, as its name indicates, happens during pregnancy, usually beginning quite late in pregnancy, in distinction to the form of diabetes that is already present before pregnancy begins. While preexisting diabetes is relatively uncommon, with a prevalence of about 5/1000 pregnancies, gestational diabetes is quite common, constituting as much as 90% of all diabetes in pregnancy (Gabbe et al. 1977).

The concern here with this form of diabetes is its alleged teratogenicity. For a review of 83 articles dealing with this topic published before the year 2000 I refer you to Kalter (1998), and once more to that invaluable compendium of knowledge, my book on diabetic pregnancy (Kalter 2000, pp 65–6); in addition to which two recent papers will be given special attention.

A multihospital-based study was made in Spain in 1976–95 of congenitally malformed children born of gestationally diabetic women, i.e. those in whom glucose intolerance developed or was discovered during pregnancy (Martínez-Frías et al. 1998). Of the children with major and/or minor anomalies found at birth 1.9% had mothers with gestational diabetes. The frequency of unspecified cardiovascular defects in these children, 6.3%, was compared with that, 5.2%, in children whose mothers were nondiabetic, an unimpressive difference. A population-based cohort study in South Australia in 1986–2000 compared heart defect frequency in gestational and preexisting diabetes, finding it to be 9.2/1000 vs 12.9/1000 respectively (Sharpe et al. 2005). Also see negative findings in Åberg et al. (2001), mentioned above.

The unavoidable conclusion is that gestational diabetes is not, and in fact cannot, be teratogenic, for the simple reason that the disturbance in carbohydrate metabolism that is its hallmark appears far too late in pregnancy to be able to disturb embryonic development. This was even noted by the authors of the Australia study just cited, who said that "gestational diabetes occurs too late in pregnancy to be a direct cause of congenital anomalies." 'nough said.

## RETINOIDS

The story of the teratogenicity of vitamin A and its related substances was told in great detail, as you might expect, in my compendium (Kalter 2003, pp 210–5). Early on, there were scattered reports of infants with a variety of craniofacial, cardiovascular, urogenital, and other malformations of women taking huge doses (up to 60,000 units daily and greater) of vitamin A during pregnancy, mostly for dermatologic conditions and breast fibrocystic disease. A later report of a large number of pregnancies of women taking even greater amounts noted children with very few malformations, none of kinds later associated with retinoids.

In 1982 an isomer of a vitamin A analogue, 13-*cis*-retinoic acid, largely free of side effects, commonly called isotretinoin and with the brand name Accutane, was registered in the US for oral treatment of severe recalcitrant nodular acne, a common ailment of adolescence and older ages. Because retinoids were well known animal teratogens Accutane was contraindicated for use during pregnancy, and recommended only to women taking effective contraception before treatment began.

Despite this warning its accidental use resulted in the births of malformed infants, noted in detail afterward to have a characteristic set of defects, given the name retinoic acid embryopathy syndrome, among which were conotruncal heart defects and aortic arch abnormalities (Lammer et al. 1985).

It is a remarkable fact, and perhaps unique, that the pattern of malformations caused by retinoids in humans is extraordinarily similar to that induced in animals. In experimental studies of hypervitaminosis-A teratogenesis the most frequent malformations induced were abnormalities of mouth, ear, and thymus, those of the thymus being the first occurrence of abnormalities of this organ produced experimentally (Kalter 1960, Kalter and Warkany 1961).

The present apprehension concerns the continued use of accutane, which by early 2000 was estimated to be the most widely used teratogenic drug in the US, with about 2.5 per 1000 women of ages 14–45 taking it in 1999, giving its use a fearful prospect. A survey conducted by Boston University found that about 40% of women of reproductive age in 1989–99 were being treated with isotretinoin with approximately 900 pregnancies occurring, the outcomes in them not yet having been fully reported it seems (Anon. 2000).

The topical product, Retin-A, does not appear to be teratogenic. It was applied to women in the first trimester in 1983–2003, without occurrence of minor and major congenital malformations characteristic of the retinoic acid syndrome (Loureiro et al. 2005).

## ACE INHIBITORS

The class of medication given the ultradescriptive designation, angiotensin converting enzyme, or for short, thankfully, ACE inhibitors, used primarily for hypertension, had been contraindicated for use in later pregnancy, but recently was also found to be harmful to conceptuses exposed in early pregnancy (Cooper et al. 2006). This finding was based on medication prescription information obtained from Tennessee Medicaid data linked to vital records and fetal death certificates of infants born in 1985–2000. Three groups of offspring were compared: those exposed to ACE inhitors or other antihypersensive medication in one or more more months of the 1st trimester only, and those not exposed to such agents.

The frequency of congenital malformations not related to chromosomal abnormality or clinical genetic syndrome, in unexposed infants was 2.9%, including 10.1/1000 with heart defects; in those exposed to other antihypertensive medication it was 2.0%, 10.0/1000 heart defects; and in ACE exposed ones, 7.6%, after omitting inadmissible ones, 43.1/1000 heart defects. Unfortunately, the defects in only the ACE medicated group were specified. Six of its nine heart defects were atrial septal defects, all but one associated with other heart defects, two were patent ductus arteriosus (these may have been related to the smallness of black babies generally; blacks were almost half of the subjects), and the last was a ventricular septal defect.

The relatively high heart defect frequency in the first two groups may indicate some overzealous diagnosis. Despite precaution to preclude it, medication may have been taken before pregnancy began. The particular ACE inhibitors (several are available) and antihypertensive drugs were not specified. Chronic illness was equally common in the medicated groups, but as noted, the intensity of hypertension

may have been greater in the ACE-treated one. These findings require confirmation. Use of ACE inhibitors during pregnancy will need careful monitoring.

## THALIDOMIDE

Saving the worst for the last, we come to what was the most cataclysmic teratological happening of the 20th century: thalidomide, a seemingly harmless therapeutic substance, that caused horribly severe congenital limb malformations, as first announced in late 1961 and early 1962 (McBride 1961, Lenz 1962). These abnormalities, of a sort usually extremely rare, known as reduction deformities, had occurred in thousands of children in many countries around the world, perhaps over 3000 in Germany alone, the country the product was first marketed in. The reason for the wide dimension of the problem was that thalidomide was a popular over-the-counter sedative taken by a large number of women during pregnancy.

The limb defects were by far the ones most often caused by the drug, the ones most dramatic and sensational. But they were not the only ones, heart defects were also found. The earliest detailed descriptions of malformed children barely mentioned heart defects, noting only one or two such occurrences (e.g. Leck and Millar 1962).

A compilation of all malformations in almost 100 children born in England and Wales whose mothers had taken the drug in January 1960 to August 1962, when its sales ceased, indicated a heart defect frequency of 50/1000 children (Anon. 1964). Almost two-thirds were dead, almost all with limb defects, but few specified as to heart defect type.

Other early studies of heart defects in children exposed to the drug prenatally found very high frequencies of a variety of such defects, 172/1000 in one study in Hamburg (Kreipe 1967), 183/1000 in another Hamburg study (Keck et al. 1971), and 91/1000 in Leeds (Smithells 1973).

About 150 infants were affected in Sweden, the drug being available in that country in 1959–61, perhaps one-third of whom died in infancy (Miller and Strömland 1999). Medical records of the defective children still alive in 1987–9 indicated that 81/1000 had cardiovascular defects, ventricular septal defects and others. No other more recent reports of thalidomide teratogenesis have been located.

Thalidomide teratogenesis ceased, it seems, as soon as, by governmental direction, it was withdrawn from the market in 1961 or soon afterwards. Thereafter, for many years, its use was banned. But in the 1990s a recrudescence occurred when numerous beneficial effects of the drug were found in many diseases, such as leprosy, various dermatological conditions, certain malignancies, immunodeficiency diseases, etc. This growing use set off alarms, of course, and made safety matters of prime importance. For a current view of these matters see www.mayoclinic.com/health/thalidomide/HQ01507

CHAPTER 19

# SUMMING UP, COMMENT, AND LAST WORD

The ultimate goal of course should be to prevent heart defects from ever happening. This may be never-never-land stuff, but who knows? So what might be possible now? First let's see what is known of their causes, supposed and otherwise; and of what the impact of the best known of these is on heart defects as a whole. A conjecture mentioned above posited that all of them, all the individual single genes, chromosomal aberrations, and discrete environmental agents that cause or have some part in causing heart defects, all together might be responsible for only a small share, perhaps 10%, of all cardiovascular malformations. It's anybody's guess how much more than this paltry amount will be augmented by micro-genetic analysis and environmental discoveries yet to be made in the present century. But who knows?

Of the discrete environmental entities acknowledged today to have such a teratogenic role–rubella, thalidomide, phenylketonuria, antiepileptics–the dangers threatened by them have vanished, been eliminated, or minimized by time, and hopefully will be still further modified by human ingenuity. Whatever portion of defects they have been responsible for it may be expected will be history before long.

What is confronted then is the task of explaining the great majority of heart defects, and as a matter of fact, all congenital malformations, since they also largely share this etiologic construct; the standard and favorite grab-bag, multifactoriality, comprised of a polygenic fraction, i.e. the combined or additive effect of some sort or number of genes that provide the proclivity, and the 'environment' (as everything that is not genetic must be), the precipitant, which tranforms the tendency into actuality. Let us examine this proposition.

As applied to experimental teratological situations the proposition is a simplification, since one component of the dramatis personae, the environmental moiety, the 'teratogen,' is no mystery. However, in nature, so to speak, the environmental part of the equation is as unknown as the genetic bed it impacts. The latter, being even more vague, has largely been ignored, while the former, seemingly more approachable, has been probed and dissected, to the extent that human imagination has allowed. But to no avail, it seems, and none of the etiological handmaidens considered has been decisively and conclusively found to be of the least help in getting closer to the basis of defect manifestation. So may it not be construed that

this environmental, this nongenetic, part of the picture is also internal, just as is the predisposition within us, and that is where to seek it.

Admitting the paucity of ideas at present, how, with current knowledge and techniques, what feeble steps can be taken to further mitigate and disallow congenital malformations of the cardiovascular system? Some few and partial answers were hinted at in pages above, improved medical care, pre- and postnatal surgical innovation, selective abortion, none the breakthrough.

The great decline in the rate of infant mortality during the last century slowed in the 1980s, largely because of the slowdown in preventing prematurity and treatment of seriously ill infants (Anon. 1989). Heart defects, the most frequent of all congenital malformations, forming a large part of infant deaths, shared in the slowdown. The advance when it resumed, saw a marked reduction in the final decades of the century, as well as an increase in the mean age at death, suggesting a greater life span of persons with heart defects (Boneva et al. 2001).

These small beginnings have left tough nuts yet to crack, some of which may similarly yield to medical innovation; but then with a further residuum perhaps left for future thinkers to deal with.

It may happen, at some far distant time, that molecular engineering will find a way to deactivate genes for teratologic susceptibility or perhaps even excise them from the genome. But until that time comes, a big question to ponder is, should the implications of successful therapy of heart defects, such as were voiced by Van Praagh (1973), be a concern. That is to say, to the extent that heart defects have a hereditary basis, rescuing the genes that cause or have a part in causing them will, it seems to follow, in time lead to their increased presence in the population; and thus once again a medical benefit will threaten a deleterious consequence. How worried need we be though? The pessimism expressed in Van Praagh's learned sounding and amusing article, that 'genetic pollution' is overwhelming us and calls for vigorous action, has as its resolution a conventional and mostly distasteful repertoire, counseling, sterilization, abortion.

Heart defects have been around for a long time, it cannot be doubted. And have been responsible for deaths all during this period, it cannot be doubted. Yet as Ecclesiastes says, All the rivers run into the sea, Yet the sea is not full. From which it can be read either that new mutations of single genes of major significance for heart defects continually replace those eliminated through death; or that the complexity of heart defect etiology is such that death of affected persons has a negligible effect on the 'genetic load,' and that is so because the vast proportion of the genes that participate in the multifactorial equation go merrily along from generation to generation never exposed to the microenvironmental stuff that bring about defects.

These and many other matters of great moment will be further discussed in the second part of this work, on congenital malformations of the central nervous system.

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