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 communicable 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 birth-weight, 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 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 foetuses, 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 foetal 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–reming 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
CHAPTER 6

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 meyelomeningocele 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

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

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 novelty 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, further 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 |
|-----------------|--------|--------|--------|--------|--------|
| 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 |
|-----------------|--------|--------|--------|--------|--------|
| 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 phenomena 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 elsewhere 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 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 correctable.

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 valuable, 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 stemmed 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—though 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 improvement 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 questionnaire 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 long-term 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 each other. 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.