Mortality and Maldevelopment

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Part II: The Saga of Neural Tube Defects

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Chapter 1
Introduction: Basic Stuff

To Begin with, Infant Death

Years ago a book of mine was published on the teratology of the central nervous system (Kalter 1968). Its subject, as its subtitle indicates, was congenital malformations of this core of existence, in laboratory, domestic, and other animals. Now, many years later, I return to this subject, but this time to consider the problem as it relates to human beings.

Congenital malformations, as by now no one needs reminding, are structural departures from the usual pattern of prenatal development so extreme as to have terrible consequences: death before or soon after birth, severe physical disability, and marked cosmetic alteration. But first and foremost, because malformations so often cause or are associated with death, it is with death as seen at birth or soon after that this work begins. Prenatal death, a subject all its own, will be considered later in these pages.

But it is death during the first year of postnatal life that overshadows all, and its history, its nature, the reasons for its occurrence, in all its facets, have been examined in exhaustive detail by numerous writers. What does it mean, why this preoccupation? A persuasive argument for this concern was expressed by a British medical officer about 100 years ago, when he said that "infant mortality is the most sensitive index we possess of social welfare and sanitary administration" (Newsholme 1910). This concern, that is, because young lives are fragile and vulnerable to hazards that older ones can better withstand. But while the death of infants is a measure of the shortcomings of society, a preeminent pediatrician of his day felt the need to add, that it is "on the physical, intellectual and moral strength of the children of today the future depends" (Holt 1913).

Infant mortality as a gauge of living standard showed in time that it has its limits. So while children depend on society, society in turn depends on children, as seen when mortality decline stalls. In previous times, as records tell us, the rate of infant mortality was incredibly high; and then began a remarkable plummeting at the start of the last century, in some parts of the world more, in others less. But the reasons for the decrease were not uniform, some causes of death yielding to alleviation or prevention, while others were resistant. For a short review of this topic see the first part of this work (Kalter 2007).

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The sorts of causes of infant mortality that yielded were mostly of outer origin, in the common parlance, environmental, associated especially with infectious disease and socioeconomic condition; while the persisting causes were generally (qualification, qualification!) of inner origin, located in the prenatal organism and its maternal envelope. This shift in the mortality spectrum brought one particular cause of death, congenital malformations, unpreventable and significantly lethal, into greater prominence.

Early Death Matters

Before continuing it will be useful to consider briefly a few of the basic definitions regarding early death, dealt with in more detail in the first part of this work (Kalter 2007); this should not be amiss, since some but it is hoped not too many years will have elapsed between the publication of that and this one. Death of the unborn and the newborn are major concerns of this work, and some of the reasons for death in the different divisions of the span from conception to infancy will be dwelt with below; but first they must be described.

A major division point is the 20th week of pregnancy, because that is now considered when viability begins, i.e. the time in prenatal life when the unborn are capable of independent existence. First definition: Death before this time is called spontaneous abortion, and death then and afterward is called fetal death.

Abortion will be given its due when appropriate below, but attention first turns to fetal death. For reasons outlined below, fetal death is in turn divided into early and late, 20–28 weeks and 28 weeks and more, respectively. The latter, given its own name, is commonly called stillbirth. The frequency of stillbirth is reckoned as the number per 1000 total births, i.e. stillbirths plus livebirths.

For various practical reasons death of liveborn children during the first year of age is divided into death in the first 4 weeks after birth, called neonatal mortality, and death in the remainder of the year, postneonatal mortality. And again for practical reasons, neonatal mortality is itself divided into early and late, namely, in the 1st week, and in the 2nd through 4th weeks after birth. The frequency of infant death is reckoned as the number per 1000 live births.

Conceptualizing this early period of life as having these segments had the benefit of allowing them to be considered individually, and major differences between them in rate and cause of death to be discerned.

Perinatal Mortality

It was especially the conceiving of fetal and neonatal death as each being divisible into early and late that led to recognizing commonalities they shared. The revelation in this respect being that the causes of late fetal death and early neonatal death were

greatly similar. As worded by Sigismund Peller, who had this insight, “stillbirths and deaths which occur within a few days after birth have in common a complex of causes which differs from the pattern in older infants” (Peller 1923, 1965). From this perspective these deaths were seen to form a unit, and in recognition of this fact were given its own name: perinatal mortality. And recognition of this similarity led to the further discovery, already implicit, that the causes of perinatal mortality were largely different from those of earlier and later deaths. Making this concept concrete, what separates perinatal from later infant death is that most of the causes of the former originate prenatally while those of the latter have a significant postnatal component.

This distinction immediately directs attention to the subject here, that of neural tube defects, and to the fact that such conditions must have prenatal origins. But before going further let us glance back at former times and begin with a brief recounting of records of occurrences of these abnormalities from the past.

Chapter 2
Neural Tube Defects

Neural Tube Defects in History

Differing from archeological and artifactual records of skeletal remains and errors of twinning, which are relatively abundant, ancient records of abnormalities of the central nervous system are scarce.

[What must immediately be commented on are older reports, as well as newer ones, of abnormalities of the spinal column erroneously labeled "neural tube defects." Mistaken instances given this name were actually anomalies of skeletal elements of the spine only, and not truly malformations of the nervous system. Further misconceptions are discussed below.]

The first observation it seems of one of the prominent neural tube defects, spinal bifida, was that of the Netherlandish anatomist Nicolaas Tulp in his *Observationum medicarum* of 1641, containing a sketch of an infant with what the author called "spina dorsi bifidi," i.e. the condition now called spina bifida; which as Ballantyne noted, "from the accompanying description and illustration was evidently an example of lumbo-sacral rhachischisis…" (Ballantyne 1904, p. 285). Much was written about such malformations in the 19th century, which saw numerous examples of it, many of its varieties mentioned and described in this work of Ballantyne's.

About the two notable figures mentioned here, a bit more must be said. First, Nicolaas Tulp (1593–1674), born in Amsterdam, died in The Hague, lecturer in anatomy and surgery in Leiden University, immortalized by Rembrandt in his painting The Anatomy Lesson of Dr. Nicolaas Tulp, which is in the Mauritshuis in the Hague, showing Tulp lecturing and demonstrating before a dissection table on January 31, 1632. He was born Claes Pieterzoon, later adopted the name Tulp, meaning tulip, some time before he was 38-years-old, and took it as his symbol, even having a representation of it carved into the façade of his house (Goldwyn 1961). One can't help wondering if this name change was related to the tulip craze, sometimes called tulipomania, that was sweeping Holland at that time, and engaged Tulp, as the scion of a prosperous merchant, supplementing his medical interests, and caught him up in the speculative fever swirling around cultivation of new varieties of that then exotic flower. About the likelihood of this supposition I have succeeded in discovering nothing.

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The other is John William Ballantyne (1861–1923) of Edinburgh, perinatologist extraordinaire, known especially as the author of the magisterial two-volume work on the pathology of the fetus and embryo, 1902–4; and as the editor of the short-lived Teratologia: A Quarterly Journal of Antenatal Pathology with Reviews of the Current Literature, 1894, which ceased publication after its second volume, owing to paucity of subscribers! We shall return below to his comments on this malformation.

The next record of neural tube defects, about a half a century after Tulp's, was made by a 17th century midwife in Friesland, Holland (Schrader 1693–1745). In her experience of delivering more than 3100 children in urban families over the course of nearly 50 years she noted several instances of central nervous system malformations, an anencephalus, two spina bifidas, and a myelomeningocele with microcephaly. Here in translation, of course, is her graphic description of an anencephalus combined with spina bifida: "I examined the case. But oh heavens, how horrified I was. The child had no head. In place of that a swelling like a flat turnip, with sharp bones with thorns set around it. And the child had on its back a circle like the palm of a hand…there was a wall around with an opening to the inside, there was a membrane grown over, containing a bloody water."

As for other olden recordings of anencephalus, "the master monstrosity of this part of the body," as Ballantyne labels it in his valuable compendium of teratologic information, there were a goodly number of mentionings from the 16th to 19th century; and finding it to be "relatively…common," comments that he himself saw it in 14% of 325 cases he examined (ibid p. 332).

But all these writings and notations were by far anteceded by an occurrence in ancient Egypt of a defect that was at first thought to have occurred in a monkey; the occasion of whose discovery was inscribed by Geoffroy Saint-Hilaire (1832–7, vol. 2, pp. 363–5). My translation of the relevant passage, however infelicitous, was placed almost at the end of my 1968 book, as cited earlier, and is placed near the beginning of this one:

> A mummy newly brought from Egypt by M. Passalaque, and belonging to the beautiful archeological collection of that learned traveler, was in 1826 subjected to examination by my father. It came from the catacombs of Hermopolis, the tomb ordinarily of sacred monkeys and ibises [desecrated during Napoleon's Egypt campaign]. A clay amulet, crude but a faithful representation of a monkey, the cynocephalus of old, had been found near it; and the pose of this figurine was exactly the same as that of the mummy itself. It was concluded from all these signs that the bandages hid a monkey. But as it appeared to differ by its size and form from the other monkeys buried with it, an interesting scientific discovery was expected and a close examination of it was requested by my father. To the great surprise and astonishment of all, the examination revealed the features of a human fetal monstrosity. [There follows a description of it, which clearly labels it an anencephalus. He continued:]
>
> We see in effect a human anencephalic excluded from human burial. Though born of a woman, it resembled an animal, but a sacred animal, and of which the religion commanded a pious preservation of the remains. [Thus it was embalmed and buried in the cemetery for animals.] Why all these honors of embalmment accorded to a being that was denied human entombment? Without doubt because this monster, monkey born of a woman, to the eyes of the Egyptians, was one of those prodigies, cited so often by ancient authors, whose apparition presaged celestial vengeance and threw entire populations into terror.

Leaping ahead, in contemporary times anencephalus especially has been abundantly noted and its development decribed (for which see e.g. Erskine 1955).

Normal Neural Tube Development

Let us plunge into our topic and discuss the malformations of the central nervous system this book is devoted to. This master component of the body, the central nervous system, is prone to a large number of developmental errors, congenital malformations, of which the major and incomparably most fundamental ones concern defects of neural tube development.

The primal role of the central nervous system in the economy of the body is denoted by its being among the first parts to develop in the embryo. The earliest step of which consists of a process broadly called neurulation—whose tissue, cellular, and molecular bases are still only poorly understood (Colas and Schoenwolf 2001)—at whose completion a hollow structure, the neural tube, will have been formed, extending the length of the embryo.

But to backtrack a bit, what will become this tube starts out as a flat area, the neural plate, in the mid-dorsal line of the embryo. The plate then sinks in to form a groove—recognizable by about 17–18 days of age—whose lateral edges, with continuing development, grow, meet, and fuse dorsally, the fusion occurring both forward and hindward, to form the tube. Closure is completed anteriorly, with disappearance of the last vestige of openness, the anterior neuropore, at the fertilization age of about 23 days (18–20 somite stage) and caudally with that of the posterior neuropore, at about 25 days of age (25 somite stage). The tube then differentiates into a short, broad anterior portion, which becomes the brain, and an elongated posterior portion, the spinal cord. For a detailed description of the early histogenetic pathways subsuming the formation of the neural tube, see Källén (1968). Following closure of the posterior neuropore the tube continues to grow rearward connecting with a solid structure which by a canalization process itself develops a lumen (Lemire 1969).

The ontogenesis of the neural tube thus occurs in two stages, a primary one, with formation of the already described tube, and a secondary one, resulting from this canalization, as it was termed (called cavitation by Müller and O'Rahilly 1987; though "tunneling" seems even better). [Incidentally, the term "canalization" had already been applied to specific developmental activities, designated "pathways," by Waddington in 1957.] More recently, two and only two sites of fusion (a term preferred to closure) of neural folds and two neuropores were found in human embryos (O'Rahilly and Müller 2002).

Failure of Closure

But the delicate and elaborate process of closure sometimes fails, the neural folds do not meet, fusion does not occur, the groove remains open, and serious malformations ensue. These malformations, those that directly result from this failure of closure (see Dekaban 1962 for a detailed description of the malclosure process, and Smith and Schoenwolf 1997 for an exposition of the cellular and molecular mechanisms responsible for normal neural tube formation), form a family of abnormalities, which, to anticipate later pages, are often regarded as etiologically, but

imperfectly, related, because of their many shared epidemiological features. One of them is anencephalus, due to failure of closure in the anterior or brain region, and spina bifida, that in the posterior or spinal region. These are not the only congenital malformations of the central nervous system, but they are by far the most common, conspicuous, serious, and intriguing.

[We take a moment to mention a different idea. It was once contended that neural tube defects do not result from failure of the neural folds to close, but from their reopening or damage at some later time (Gardner 1960, 1961). This alternative explanation has been discredited by various lines of evidence—experimental studies with rats and mice and studies of anatomical features of human embryos (see Dekaban 1962, Nakano 1973 for details) and is no longer taken seriously.]

Defining Neural Tube Defects

At this point we enter the contentious area of defining the terms to be used in this work and describing the entities they refer to. To this end it is necessary to distinguish the two general kinds of errors of development that the neural tube is prone to; labeled neurulation defects and postneurulation defects by Lemire (1988), or as I would designate them, closure and postclosure defects. It is the former, anencephalus and spina bifida aperta, to which in this work the appellation neural tube defects, or NTD, as they are so fondly denoted, is restricted (whether to refer to NTD as singular or plural is a puzzle, sometimes it is the one, sometimes the other; the reader must puzzle it out for himherself).

Defining anencephalus should not be a problem, it is unmistakable and conspicuous and lethal. Further considerations regarding it will be noted below. This is hardly true of spina bifida. By itself, it should be explained, spina bifida is a generic term merely connoting a split or "bifid" state; and what is split may be skeletal or nervous elements. In the former the anomaly consists of midline dorsal defects of the bony spine, i.e. absence of the posterior neural arches, but which are still skin covered and thus covert, giving it its name, spina bifida occulta. This anomaly may have repercussions in later childhood, but is itself not fatal; and hence is not of further interest here. When however the bifidity involves neural tissue the condition is known as spina bifida aperta (i.e. open—visualize an open book), or sometimes, most lexically vivid, myeloschisis (myelos, marrow; schisis, split), and is a lethal or seriously debilitating abnormality. These, then, anencephalus and spina bifida aperta, are the abnormalities that result from the neural folds failing to close and form a tube.

In addition to these defects there are others that qualify as neural tube defects, but not as due to failure of neural tube closure. (This is a source of confusion.) These defects, meningocele and encephalocele, are localized, later arising, i.e. postclosure, and relatively less frequently occurring, consist of external saccular protrusions of meningeal tissue through skull or vertebral interruptions. A generic term for these

protrusion defects is spina bifida cystica, one that has occasionally been erroneously used as synonymous with spina bifida aperta.

[Let me quote a description of what was termed spina bifida cystica, as an example of an accepted view and definition of this defect (Doran and Guthketch 1961). "We define spina bifida cystica as a congenital anomaly of development in which there is a defect of fusion of the posterior neural arch of one or more verterbrae accompanied by a protrusion of the membranes of the spinal theca, with or without the cord and nerve roots, beyond the limits of the spinal canal…" The definition then divides cases into meningocele, composed simply of herniation of the dura, and myelomeningocele, in which the sac also contains parts of the spinal cord and nerve roots. Thus, here, even in the latter forms, the defect does not include malclosure of the spinal cord itself, which is the strictest, and correct, application of the term "cystica."

More explicit are the descriptions given by Warkany (1971, p. 272): "If there is an external saccular protrusion, one speaks of *spina bifida cystica* (italics in original). Saccular enlargements protruding through osseous defects of the vertebral column that contain anomalous meninges and spinal fluid but do not have neural elements affixed to their wall are called meningoceles. If the spinal cord or nerves are included in the formation of the wall, the anomaly is called myelomeningocele."] Here, thus, is reinforced the fact of these defects being of nonclosure origin.

It is especially these saccular anomalies that authors, in reporting on spinal tube malformations, have often been vague or unclear about, without identifying these varieties or their comparative frequency separately. In this work, when listed separately, they were excluded from the tally of neural tube defects of the aperta variety. Also, for brevity's sake, in this work unless otherwise noted, the term spina bifida refers to spina bifida aperta.

Cystic and noncystic defects have often been indiscriminately labeled as one. Which is understandable since in almost all instances the defects noted in reports are those seen at birth, when their appearance usually conceals their original state; the misidentification due to the degenerative changes that occur in the months between the time the defect arises early in embryonic life and when it is seen later. Experimental studies and human embryological observations leave no doubt that defects described as containing spinal cord or nerves result from transformation of the original apert condition (Warkany et al. 1958, Warkany 1971, pp. 278–9).

Since few human specimens have been seen at the prenatal stages during which the transformation occurs, an understanding of its processes has necessarily largely depended on experimental material. A very early human embryo with myeloschisis, the smallest one with this anomaly seen up to that time, substantiated the degenerative interpretation (Lemire et al. 1965).

To return briefly to anencephalus, it too undergoes degenerative processes during the long fetal period, such as those experienced by the spinal lesion, which as revealed by studies of experimental animals and early human embryos, transform the original malformation, exencephaly, an everted brain, lacking skeletal envelope, into anencephalus "from the state of encephaloschisis" (Warkany 1971, p. 191).

These facts underscore that the writer of a broad survey such as this one is in the hands of those who have written the articles he attempts to digest and interpret; that he must rely on what these writers say they have discovered, and these in turn are often forced to rely on what they have found in summaries and reports of one sort or another left by various others. Thus, in a word, the writer of a broad survey must warn his readers of these nebulosities and beg their pardon for the imperfections of the record, and of course for his own fallibilities.

Before we leave this matter, let me give the reader an example of the blurring between boundary lines of the many different forms and degrees of anencephalus and spina bifida, which were then aggregated into the one or the other, simply because these are the ways such defects were entered into hospital records. "The term 'spina bifida' (the writer explained) includes the diagnoses of spina bifida cystica, meningocele, myelomeningocele, myelocele, rachischisis, hydromyelocele, hydromeningocele…encephalomyelocele, cranium bifidum…hydroencephalomyelocele, meningoencephalomyelocele… Anencephalus includes acrania, hemianencephaly, hemicephalus…'monster'…" (Haynes et al. 1974).

Hence buyer beware, especially with respect to spina bifida: the present writer, often given no certain assurance of its validity, has had to accept the otherwise unqualified designation of a defect as a spina bifida as being a spina bifida aperta.

Definition Differences

After all this, what hopefully will be some final words about definition must be given. There are generally it seems, at least, two schools of thought about what spina bifida consists of, one inclusive, one exclusive. The first is typified by Leck (1977), the other by Warkany (1971). Leck, an eminent epidemiologist, says the following. "The neural tube defects are those that arise when the closure of the neural tube and its submergence within the mesoderm are disrupted. The practice in most epidemiological studies…is to divide these defects into two mutually exclusive groups—'anencephaly'…and 'spina bifida,' comprising all other cases of meningocele, myelocele, and encephalocele…" (Leck 1977, p. 250). Thus, while on the one hand he says that NTD result from disruption of neural tube closure, on the other he includes entities, meningocele, myelocele, and encephalocele, which as descriptions of these defects above indicate, do not stem from such malclosure.

Warkany, a clinical pediatrician and animal experimenter, distingishes between spina bifida aperta, i.e. 'open' neural tube, and spina bifida cystica. The latter, as the term cystic indicates, is characterized by "external saccular protrusion…through osseous defects of the vertebral column that contain anomalous meninges and spinal fluid but do not have neural elements affixed to their wall…" (Warkany 1971, p. 272). The cystica defects are thus differentiated from open neural tube by morphology and pathogenesis, as well as by etiology and epidemiology.

A Word about Etiology, etc.

A word about etiology, the cause(s) of neural tube defects. About a century ago there was certainty that monsters, as anencephalus was sometimes designated, were "not due to germinal and hereditary causes but are produced from normal embryos by influences which are to be sought in the environment" (Mall 1917, p. 70). That view, influential in its day, is remarkably similar to the view held today.

As so much else in the world, the causes of neural tube defects are divided in two, but in this case not equally. In the much larger part are malformations whose causation (for now) is unclear, currently explained as the product of interactions of vague elements out there in the environment, and inherent tendencies (predilection, proclivity, propensity, you name it), also for the moment vague; the whole construct given the unsatisfactory designation multifactorial. Thus for neither of these parts are there recognized specific components, proximate or otherwise, you can put your finger on.

And then there are the others, the far smaller moiety, those not having the character of multifactoriality, but due to individual identified factors, single causes, mutant genes and other genetic disorders, chromosome abnormalities, teratogens, etc., of a heterogeneous nature. What percent fall into each of these divisions? Based on actual findings, a modest study had the latter at an appreciable 12%, largely because many of the defects had recognized phenotypes (Holmes et al. 1976); and another, a more comprehensive study, also finding heterogeneity, had it at a more humble 0.6% (Khoury et al. 1982). The truth probably lies somewhere in between. The point however is that the great majority of NTD are without known causation, for now. And it these conditions, sometimes known as nonsyndromal, that this work will almost entirely be concerned with.

A note regarding defects occurring together: Spina bifida is occasionally combined with anencephalus, but because of etiological similarities and because the latter is by far the more severe defect the combination is classed as anencephalus. A different type of example is the frequent occurrence of hydrocephalus with spina bifida. In this case the defects are not coincident, the former being a consequence of the latter, and thus the combination is listed as spina bifida. Isolated hydrocephalus not being a NTD is virtually disregarded here.

It's worth considering a recent article, fortuitously come to my attention at this moment, entitled "Are encephaloceles neural tube defects?" (Rowland et al. 2006). The authors' argument in support of this malformation being a NTD is that "encephalocele shows…similarities to spina bifida or anencephaly…with respect to characteristics, temporal trends, and impact of folic acid fortification." Even were these criteria to be accepted as established, they are hardly relevant. Even the authors, although hesitatingly, put their collective finger on the reason for this, when they say that its "underlying mechanism may differ from that of spina bifida…and anencephaly." But there is no 'may' about it: encephalocele stems from a localized herniation and not from failure of neural tube closure.

One further word—this is getting tiresome—regarding these questions, stemming from prenatal detection of NTD, the topic itself discussed in detail below.

Fetuses with NTD may be identified by the increased presence in maternal serum of alphafetoprotein (AFP), a normal fetal product which leaks into amniotic fluid and then reaches the maternal circulation. This leaked substance comes from exposed neural tissue, i.e. an open neural tube, which thus emphasizes that malformations whose basis is lack of fusion is the ultimate consideration.

Now, what about the 'cause' of this failure of closure? Initially it may be due to abnormality of induction by the tissues from which the neural plate originates, which is another way of admitting ignorance. Pages have been consumed in describing these malformations, their variations in degree, form, type, site, etc. (e.g. Ballantyne 1904, p. 285 et seq, Warkany 1971, p. 189 et seq, Lemire et al. 1978), and will be considered here as becomes necessary. Of 'cause' in the other sense, that which is even anterior to the proximal one, its precipitant, just as little for long was known, which may still be the case. These are matters to be gone into below.

A word about NTD, especially anencephalus, in laboratory animals, due to single mutant genes in laboratory mice, or experimentally induced by numerous chemical agents and other means (Kalter and Warkany 1959, Kalter 1968). We will return to this subject later. It should only be mentioned here that the protrusion of the brain in such instances, as noted above, is called exencephaly, which aptly describes the defect in young fetuses (and in human embryos as well, when seen in early abortions). The days in utero till birth, more so in humans than in other animals, through months of deterioration of unprotected nervous tissue, also noted earlier, usually leaves only vestiges of brain, transforming the defect at birth into anencephalus, a misnomer however, since brain tissue is not entirely destroyed.

One final final word, regarding the would-be universal definition of neural tube defects, those listed by the International Classification of Diseases. The ICD, as it is known, if I may quote from the World Health Organization (WHO), "is the latest in a series which has its origins in the 1850s. The first edition, known as the International List of Causes of death, was adopted by the International Statistical Institute in 1893. WHO took over the responsibility for the ICD at its creation in 1948, when the Sixth Revision…was published." (see http://www.who.int/classifications/icd/en for a history of the development of medical classification of diseases.)

Since ICD-6 there have been periodic revisions at roughly 10-year intervals, the current one is the 10th. It is of interest to inquire what NTD was considered to consist of in these versions. ICD-7, published in 1955, had four entries, only two of which are relevant: monstrosity and spina bifida and meningocele. Subsequently the list has expanded. ICD-8, of 1966, listed anencephalus, spina bifida with or without hydrocephalus, and other anomalies including encephalocle. ICD-9, 1977, listed anencephalus and similar anomalies, i.e. craniorachischisis and iniencephaly; spina bifida, region unspecified or cervical, dorsal (thoracic), lumbar; and without hydrocephalus, an assortment, including meningocele, rachischisis, spina bifida (aperta). ICD-10, 2007 update, anencephalus and similar anomalies, i.e. craniorachischisis and iniencephaly; encephalocele, including variations; spina bifida, including numerous variations, e.g. hydromeningocele (spinal), meningocele (spinal), meningomyelocele, myelocele, myelomeningocele, rachischisis, spina bifida (aperta)(cystica), syringomyelocele.

What comes through clearly from this enumeration is that the ICD classification is based solely on appearance at birth. For example, iniencephaly looks like anencephalus, hence is listed together with it. But in addition to what something looks like, here we are most especially concerned with how it came to be, pathogenesis. And from this aspect iniencephaly is unrelated to anencephalus. And similarly, we see that myelomeningocele, being a protrusion of tissue superficially looks like a spina bifida, but is a different kettle of fish, not having a bifidous origin.

To conclude this didactic moment, I quote the definition of spina bifida given by the International Clearinghouse for Birth Defects: "a family of congenital malformation defects in the closure of the spinal column characterized by herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine. Include meningocele, meningomyelocele, myelocele, myelomeningocele, rachischisis." This is fine, except that we are concerned not with defects in closure of the spinal *column,* but with that of the neural tube; and several of the included items fall outside this definition.

It would be well to conclude this space devoted to definition, by giving what is the most practical and most widely accepted definition of congenital malformations in all. I devoted almost the entire preface of a book of mine to attempting to deal with this contentious topic, which see not only for its historical interest (Kalter 1968). But the passage of time, it would be hoped, has lessened the confusion, and permitted the following 'one-liner' definition to cover all bases: macroscopic abnormalities of structure attributable to faulty development and present at birth. For the qualifications and exclusions see Leck et al. (1968).

The Frequency of Neural Tube Defects

It is impossible to speak of 'the' frequency of NTD. And that is because its frequency differs and has differed in astonishingly many ways: by ethnicity (which in itself is complicated—see Senior and Bhopal 1994), race, geography, time, sex, region, area, neighborhood, social class, socioeconomic status, parental occupation, longitude, latitude, season of birth, maternal age, parity, or birth order. And this does not include intergenerational factors, time-place clustering, twinning, and various risk factors. And not to be overlooked, differences in abortuses, perinatal deaths, and survivors. And last, and gravely problematical, is the impediment of definition, especially of spina bifida, discussed in extenso above.

It is even a question how to designate what is meant by the frequency of NTD. First of all, differing e.g. from the overall frequency of the other large component of congenital defects, those of the heart and great vessels, which regardless of this, that, or the other, have not varied much in time and place (Kalter 2007), the overall frequency of NTD is anything but uniform and constant; though as a generalization, and with hazard, a number such as 1 in 100 has sometimes been mentioned. But the sometimes indiscriminate manner the term frequency has been employed with respect to NTD, especially anencephalus, has been felt to be inappropriate since

its meaning—the general way of denoting the number of times a particular event occurs within a specified interval or among a specified group of individuals—can differ according to the particular situation.

Thus the term has sometimes been refined and more precise meanings applied, such as 'incidence,' meaning new occurrences of a particular event during a given period, and 'prevalence,' the totality of such events existing at a given time. With respect to malformations, then, incidence is the proportion of abnormal individuals born during a specified interval of time, and prevalence is the proportion of individuals of a given age or other characteristic that are abnormal. Much ado about nothing usually, since a single age group, newborn infants, is almost always the basic subject of malformation studies. These differentiative terms may be useful for instance in epidemiology, but in teratology they are merely elegant variations.

There is also the generic term frequency, which though corresponding approximately to prevalence, in referring to the number of times a specified phenomenon occurs within a specified interval, yet differs from it in encompassing not only existence but occurrence. It is the term that will be used here, simply because it doesn't carry the baggage of the others, at the risk of forsaking elegant variation.

There is an instance when any of these terms of designation may be confusing, i.e. when applied to subjects of different age and survival, spontaneous abortuses, elective abortuses, stillbirths, neonatal deaths, surviving live births, since for various reasons the frequency of malformations differs, sometimes greatly, among them (Kalter 1991). Whatever the term used, when comparing, e.g. embryos and newborns, whose rates of malformations may differ, such differences must be explicitly acknowledged.

A word clarifying designation of frequency employed below. When NTD are designated as occurring per number of births that should be taken to mean total births, i.e. including stillbirths. When the designation is given per number of pregnancies, not further defined, that should be taken as including elected abortions (and rarely spontaneous abortions, when known).

The important subject of what is called ascertainment must be mentioned. In estimating, discovering, judging malformation frequency the all-important matters of mode and method come into play. Who, what, when, where, all asked by a good newspaper reporter, must be considered in comparing results of different times, places, conditions, situations. Studies of a great variety of sorts have been made under almost an infinitude of methods and manners; and in order to compare, reconcile, and make sense of their findings these must be taken cognizance of.

Let me interrupt to bring something to the fore, a major, if not the major, theme of this work: the telling of the occurrence, in the 20th century, during an instant of time, of a major alteration, an extraordinary, perhaps a unique, biological change. Unique in being a saltation in a fundamental prenatal attribute, an inborn process, of a sort that in the normal course of events, may unfold only after the passage of eons, happened within a couple of lifetimes. And that is the virtual disappearance of a major form of an embryological error. After these flowery words, then, I say what will be done here, is to trace to the extent possible the record of the rise and

especially the decline in the frequency of NTD in the just past century to the level of further irreducability.

Death and Malformation

We start with a description of the congenital malformations this book is about, a depiction of their intensity and severity that will instantly impart their scarce hopefulness for survival. In the words of an early scholar, the "characteristic features [of anencephalus] are that the cerebral hemispheres are replaced by a mass of amorphous vascular tissue and that the vault of the skull is completely absent… A frequent additional feature is spina bifida in the cervical or upper thoracic region. In the most extreme cases, almost the whole of the neural tube fails to close" (Penrose 1957). Another, setting the stage for this book, said "anencephaly is one of the most striking congenital malformations recognizable at birth…it exemplifies the problems and difficulties of teratologic research in man" (Warkany 1971, p. 189).

Given this description, we can but wonder that conceptuses with these malformations do not all perish in prenatal life. Most with anencephalus in fact do not come to term, but most with spina bifida survive, to suffer and die later. Fetuses with these defects have different mortality eventualities however. Some large proportion of anencephalics die prenatally and are aborted, as we will learn below, the remainder almost always born as stillbirths; while death of most of those with spina bifida occurs soon after birth, as neonatal deaths. But again, it is a puzzle why many conceptuses with anencephalus, so drastic a defect, interfering as it certainly does with vital physiological functions, do survive to term. And incidentally, doubly troublesome in fact, because so far as I am aware explanations are scarce, is why fetuses with apparently innocuous malformations perish prenatally.

Let's consider early mortality in general. About the topic of neonatal and infant death, numberless and often repetitive words had been written: about how it had decreased and what accounted for it (see the first part in this series for an extended treatment of this topic). After about midcentury, when infant mortality had abated to the extent that permitted attention to turn away from causes that were more preventable or at least mitigable, to those continuing to be intractable, congenital malformation began to come into its own. But most usually only malformations as a whole and not particular ones. At any rate, this switch allowed a general phenomenon to emerge; viz, that as the infant and especially neonatal mortality rate declined, the relative frequency of deaths from congenital malformations grew, even as their absolute number was diminishing.

Chapter 3
Setting the Stage

Malformations in Early 20th Century USA

An indication of the dimension of the problem of congenital malformations as cause of early infant death in the first years of the 20th century may be gained by a brief description. One source, US mortality statistics, listed malformation in general as the cause of death beginning as early as 1910, when it was said to be responsible for 12% of deaths in the first week and 18% in the first month; appreciable, but unspecified and probably including defects today considered unacceptable for inclusion in the canon (Anon 1912).

Continuing with US data, more informative are individual reports which noted that only a small minority of such deaths were caused by deformity. This is exemplified by findings in a very large number of consecutive admissions to the Obstetrical Department of the Johns Hopkins Hospital, about 7% of which died in the perinatal period. Of these the majority were due to the usual problems of the time, toxemia, difficult birth, etc., but of them 3.4% were deformed, more than half with anencephalus and spina bifida, mostly the former (Williams 1915). [Doing a little arithmetic, I came up with a probable frequency of NTD of 1.19/1000 births, similar to later estimates.]

It is to be noted that Williams said something unusual, not only for his time but even for many years later. Not only did he record in detail what was then a relatively minor problem of the newborn, developmental anomalies, but, as well, he realized that such anomalies "originated during the first weeks of pregnancy," anticipating a general precept of teratology explicitly enunciated only years later; and hence that they were beyond the preventive capabilities of his time.

A small number of other early reports also mentioned NTD. A later one from the same Johns Hopkins unit noted that of stillbirths with assignable causes of death 3% were due to fetal anomalies, only one a NTD, a spina bifida, a low number due, as the author perceptively speculates, to "anomalous fetuses [succumbing] earlier in pregnancy" (Dippel 1934), a murky subject returned to below.

In a contemporary consideration, of a large number of consecutive births in the Chicago Lying-in Hospital, 2% died in the first 2 weeks of life, 15% with malformations,

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including several with anencephalus (unstated but probably all or most stillborn), which gave an early estimate of 0.5/1000 births (Swanson et al. 1936). There followed a period of some years when such matters were all but neglected by US investigators; numbers of fetal and neonatal deaths being stated, but malformations seldom. A report from Philadelphia in mid-century broke this silence with a bang (Murphy 1947). It will be considered in detail below; as will many other such reports.

Chapter 4
Studies in the Old World

United Kingdom and Ireland

Now we truly begin this history by turning to studies in the old world, where copious recording of these phenomena took place. Proceeding area by area we first examine what has been found in islands lying off the western coast of Europe, where study of the frequency of NTD has a long history. What makes these observations of especial interest is that these are areas mysteriously possessing extraordinarily high frequencies of NTD, which for this reason were given much attention over the years. While these were once higher than almost any other place worldwide, they varied considerably from one region to another; generally being highest in the Irish island, both north and south, and nearly as high in parts of western Scotland and the northwest and west coast of England and Wales, gradually lessening as one proceeds eastward and southeastward to the London region (see the map excellently depicting these geographical variations in Elwood 1970a).

Liverpool

We will be going from city to city and area to area, giving credit where it is due. But for a historical reason the starting place will be Liverpool, a major city on the west coast of England, because that is where the earliest known compilation regarding this phenomenon in these islands came from (Malpas 1937). It was included in a report of all congenital malformations in infants, presumably neonates, in consecutive births in 1923–32 in the Liverpool Maternity Hospital, a total of 2.10%, which included some of minor sorts. An amazingly large number of these abnormalities, just over half, comprised anencephalus and spina bifida, plus some hydrocephalus and the usually far rarer defect iniencephaly. The frequency of anencephalus per 1000 births was 3.15 (about 14% with spina bifida) and of spina bifida 2.79, in all an astonishing 5.94, or 1 in 168 births! It is pertinent to leap ahead for a moment, and note that the frequency of anencephalus in these early years of the century

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was almost identical with that found in Liverpool 27 or more years later (Smithells et al. 1964, 1968), indicating its constancy in this region during this extended period. We'll return to such aspects of the question in time.

It is puzzling that spina bifida, whose definition over the years, as we know, has presented much difficulty, was here termed a "minor malformation," in the same category as cleft lip and clubfoot, which gives one pause in trying to imagine what the defect, or defects, considered here actually was; although, as the author was aware, "spina bifida is closly allied to…anencephalus…embryologically…." Also perplexing is the fact that in this 10-year period there were a mere 13,964 births, this in an apparently major facility, the Liverpool Maternity Hospital, in a city that in 1930 had a population greater than 850,000. Can this sparse number mean that many births were domiciliary, not unusual at the time, raising the possibility that the NTD frequency in hospital births was exaggerated.

No doubt most if not all the anencephalics were stillbirths and the spina bifidas neonatal deaths, but this is not clear since age was not stated. An interesting observation was that abortion was twice as frequent in fraternities in which anencephalus occurred as in those in which it did not, a possible epidemiological strand intensively followed up later.

The etiology and associations of malformations were, for the time, piercingly dealt with by Malpas—maternal age and parity, parental consanguinity, environmental factors, malformation multiplicity, and recurrence, etc. His insights into problems still faced today are remarkable and should not be forgotten. He wrote: "…human malformations cannot be solely due, if at all, to hereditary causes…" and "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. Later reports from Liverpool will are dealt with below.

One matter is puzzling. Prompted by an entry in a table in the article by Böök and Rayner (1950), which states that in Liverpool Malpas noted an anencephalus gender distribution of 31 females and 13 males, for a sex ratio of 41.9, I diligently searched the Malpas report, word for word, but could not find a single mention of this fact. Could it be that Böök and Rayner were in communication with Malpas, by snail mail in those pre-email days? It will be interesting to keep those two figures in mind, the anencephalus frequency of 3.15/1000 births and the sex ratio of this defect, 41.9 (sex ratio is often conventionally expressed as the number of males per 100 females).

Other areas in Great Britain are reviewed below, but Ireland and its extraordinary record come first. Ireland has had the unenviable distinction of having higher recorded frequencies of anencephalus and spina bifida than almost anywhere else in