VOLUME 30

HANDBOOK OF CLINICAL NEUROLOGY

P. J. VINKEN and G. W. BRUYN

CONGENITAL MALFORMATIONS OF THE BRAIN AND SKULL

PART I

CONGENITAL MALFORMATIONS OF THE BRAIN AND SKULL

PART I

Edited by

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in collaboration with

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Foreword to volumes 30, 31 and 32

In these volumes the editors have endeavored to present a thorough and comprehensive treatise, encon passing all aspects of congenital malformations of the central nervous system and its encasing structures.

Human malformations and, in particular, those of the central nervous system, are no less perplexing today than they were twenty-five or fifty years ago. It is a disappointing fact that progress in the understanding of the etiology and pathogenesis of these malformations has not kept pace with the recent advances in clinical neurology. At a time when exciting discoveries in areas such as the metabolic etiology of disease, the immune response system, and latent viruses, justify the promise that success in elucidating the pathogenesis of a large number of neurological disorders is just around the corner, malformations of the nervous system still remain stubbornly resistant to the search for the basic defect, and hence, to their prevention and treatment. The clinician, especially the pediatric neurologist, who has to grapple with the malformation problem almost daily, is continually left with a sense of frustration and futility.

Some insight has been gained from experimental teratology which has been singularly successful in reproducing practically all malformations known to man by a variety of exogenous and endogenous agents. However, it is reasonable to predict that resolution of the malformation problem will come ultimately from molecular embryology, a field in which activity has been gaining momentum during the last few years. The recent probes into the molecular mechanism of the developmental clock which regulates cell interaction and migration during embryogenesis offers a glimmer of hope for understanding the nature of the basic defect in the malformation process.

In the meantime, progress in clinical teratology has been and is being made, though painfully slowly and with faltering steps. The genetic etiology of some malformations and the chromosomal basis of others have been recognized. For these there is hope of prevention through genetic counseling. Very occasionally, an infectious agent or a chemical is identified as a teratogen in man, but not before it has spread misery and tragedy to scores of victims and their families. Such occurrences alert us to exercise greater caution in the administration of prenatal care, and to intensify our search for new teratogens.

In the area of diagnosis and treatment success has been a little more heartening. Malformations of the nervous system are particular beneficiaries of the recently developed prenatal diagnostic techniques of alpha fetoprotein level determination and

sonography. Progress in radiologic examination and computerized tomography has opened new vistas in establishing the correct diagnosis of previously vague and ill-defined malformations and malformation syndromes. And the daring skill of the neurosurgeon has achieved, in selected cases, stunning corrective and cosmetic results. Unfortunately, these admittedly spectacular advances still affect only a small proportion of cases.

It is altogether fitting, therefore, that three of the forty-odd projected volumes of the Handbook of Clinical Neurology be devoted to congenital malformations of the central nervous system.

In our effort to design a scholarly work, one that would cover all aspects of malformations of interest to the clinician, we thought it wise to proceed from a general survey of the field to a detailed discussion of each specific malformation. Thus, a series of five introductory chapters set the stage by reviewing concepts, definitions and classification, normal developmental anatomy and histology of the central nervous system, errors in differentiation which result in malformations, etiology, and natural history of central nervous system malformations. An additional chapter of introductory nature, on human chromosomes and their aberrations, precedes the chapters on specific malformations produced by, or associated with, chromosomal defects.

Practically all types of central nervous system malformations are found as a frequent or occasional component of malformation or disease syndromes, not primarily of the nervous system. In recent years, an enormous number of such syndromes has been described in the world literature. Most of these are reports of single observations; others have not yet been recognized as distinct nosological entities. Only well-established and accepted syndromes are included here. They are presented and discussed in separate chapters: syndromes with infectious pathogenesis, bone defects, growth deficiency, metabolic disturbance and chromosomal abnormalities. In these chapters, special emphasis has been placed on the associated nervous system malformations and neurological findings.

In a work of the scope and length of the Handbook of Clinical Neurology, it is inevitable that there is some overlap and even duplication of subject matter. A little duplication is desirable and in some cases the editors have, frankly, encouraged it. It provides a new and often welcome approach, a fresh point of view. Previous volumes of this series, for example, have been wholly devoted to the phakomatoses, tumors of the brain and spinal cord, and arteriovenous malformations. But it would be well-nigh fraudulent to claim comprehensiveness in the present volumes without including chapters on these malformations simply because they have been covered in detail in other Handbook volumes. Besides, the emphasis here is on those malformations thought to be of congenital origin. It would not do to send the interested clinician who has acquired the present volumes, scrambling to other volumes of the series in order to locate and study these malformations.

Almost four years have elapsed between the initial design of these volumes and their publication. The task has been a difficult one and the course arduous, at times dishearteningly so, for editors and contributors alike, and not all who became involved in this undertaking made it to the end. We owe a debt of gratitude to the contributors whose individual and collective efforts have come fully up to our expectations. We also

wish to acknowledge the invaluable help of Jenny Kruseman, Brenda Vollers and Kris Lucas, and the editorial staff, throughout the planning and preparation of these volumes.

P.J.V.
G.W.B.
N.C.M.

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Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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CHAPTER 1

Concepts, definitions and classification of congenital and developmental malformations of the central nervous system and related structures

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Malformations are abnormalities of structure, and teratology is the branch of medical science that studies their morphology and pathogenesis.

All body systems are susceptible to malformation and, as far as it is known, to the same or similar embryopathogenetic mechanisms. The following discussion, therefore, applies equally well to malformations in general as to malformations of the CNS. Special emphasis, of course, will be placed on the latter, since they are our primary concern.

Malformations were known to the earliest civilizations, going back to the stone age. There is historical evidence from around 2500 B.C. that chondrodystrophy and other gross malformations were recognized in ancient Egypt. The Hebrews of old must have had an excellent knowledge of the familial behavior of malformations, for from it they derived empirically their laws about marriage. Aristotle, in the 4th century B.C. recognized them as results of abnormal growth. But it was not until the 18th and 19th centuries, when embryology developed as a science and embryologic research flourished, that the embryopathology and causation of malformations were recognized and were put on a scientific basis.

It is at this time that teratology emerged as a science, at first preoccupied with grotesque deviations from the normal in both directions (monsters – wonders), later to encompass the study of all malformations which presented medical problems.

During the latter part of the 19th century, teratology was purely descriptive. The beginning of the 20th century, however, ushered an era of exploration and understanding of causative mechanisms with the first of several important milestones which were to be reached at intervals of 20 years: the rediscovery of the laws of heredity in 1900, formulated by Gregor Mendel 35 years earlier, which made possible the recognition that many malformations were genetic in origin and could be transmitted from generation to generation, according to those laws.

The environmental causation of malformations, and particularly those of the nervous system, was first demonstrated by Aschenheim in 1920, when he published a case of a microcephalic child born to a woman who was exposed to radiation during pregnancy. Next came the epochal observations of Gregg (1941) which led to the discovery that rubella infection can produce a wide array of serious malformations. Finally, in recent times Lenz (1961) and McBride (1961) brought to attention the chemical induction of malformations by thalidomide ingestion.

Malformations of the CNS are common and account for between 5 and 10% of all malformations; in other words one in about 75 children is born with a CNS malformation or a disorder which

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has associated CNS malformations. Most are major, severe malformations, often lethal in utero or leading to death in early infancy and childhood, or causing severe disability throughout life and decreased life span. Only a handful can definitely be attributed to specific environmental stresses in man, though they are among the most frequent malformations induced by external teratogens in experimental animals (Kalter 1968). Some are known to be genetic in origin, due to gene mutations or chromosomal aberrations. But the majority of CNS malformations are of unknown etiology, presumably due to interaction of genetic and environmental factors. The relative role of these factors and their mode of interaction are unknown.

WHAT IS A MALFORMATION?

The discoveries of the first half of the 20th century, coupled with the recent, spectacular progress in molecular genetics and cytogenetics, brought about during the last decade and in our times, a surge of activity in all areas of research and study of malformations: taxonomy, etiology, embryopathology, pre- and postnatal diagnosis, recognition and delineation of malformation syndromes, management and treatment. The literature on all these aspects has become enormous, if not unmanageable. Yet, as Kalter (1968) points out, so seemingly elementary a task as defining the term *congenital malformation* has not been satisfactorily accomplished.

To be sure, there are the dictionary definitions, but they do little more than derive etymologically and define the word. Malformation, they tell us, means imperfectly formed, a deviation from the normal; hence, a faulty formation of structure or parts.

Nobody will argue with this definition. Beyond that, however, there is no generally accepted standard or agreement as to what is to be included under the term *malformation*. In most investigations a 'working' definition of malformation is dictated by the nature of the investigation, the size of the sample, the method of collection of information, the accuracy of clinical observation, and, in the last analysis, the opinion and judgement of the investigator himself.

Most investigators include only gross or macroscopic defects (Stevenson et al. 1950; McKeown and Record 1960; Kalter 1968); others, like Warkany (1971), would also admit microscopic abnormalities. Tatum (1961) went as far as to consider molecular abnormalities as well, on the premise that the genetic component ultimately determines every character, from biochemical to morphologic, and that development and differentiation involve an orderly sequential expression of genetically established potentialities, which results from the interaction between the genome and the environment.

Some investigators, claiming accuracy and convenience in comparing data from several sources, restrict the definition of malformations to those observed at birth (Carter 1963; Warkany 1971) while others extend the period of observation to days, weeks or months after birth, up to the first year of life (Myrianthopoulos and Chung 1974). The question of malformations in liveborn vs. fetal deaths and autopsied cases is purely epidemiologic but it adds another disputed variable to the definition.

The National Institute of Dental Research of the National Institutes of Health of the United States, convened on February 10 and 11, 1975 a panel of experts at Bethesda, Maryland, to discuss further some tentative suggestions for classification and nomenclature of malformations made at a similar meeting the previous year (see Special Article Lancet i, 1975). The panel suggested the following definition: A *malformation* is a primary structural defect that results from a localized error in morphogenesis. This is distinguished from *deformation*, an alteration in shape and/or structure of a previously formed part.

This definition is a core or dictionary definition, and on the face of it, precise and unambiguous. But it ignores the many details and ramifications of practical application in a variety of situations, which would make it universally useful. Further, it distinguishes malformation from deformity, which theoretically might be correct, but which introduces formidable practical difficulties, as we shall see presently.

The requirement of a localized error in morphogenesis implies that such error has occurred early and that the resulting malformation is present at

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birth. Both of these implications present serious conceptual difficulties.

We have been conditioned by developmental embryology to think of the developing human organism as an embryo between the second and eighth weeks, and as a fetus thereafter, and to distinguish between faulty development in early organogenesis and destructive or regressive developmental abnormalities which occur during fetal life. But there is no hard and fast line between embryonic and fetal period. The division is convenient but arbitrary, in a continuum of formation and function, at any point of which an insult may result in primary or secondary malformation. Neither is it possible to always distinguish early from late disturbance in organogenesis. Genetically determined hydrocephalus and microcephaly, for example, originate early in morphogenesis but they are often indistinguishable from those produced by such teratogenic infections as toxoplasmosis or cytomegalic inclusion disease and other diseases which produce malformations late in fetal life.

The same argument applies equally well to deformities. A *deformity* is a prenatal alteration of form or structure of a previously normally formed part. Clubfoot and torticollis are examples of deformities. Among nervous system malformations, some frontal encephaloceles, brain changes due to skull malformations, and even diastematomyelia would be considered deformities. But again, in many cases it is extremely difficult to distinguish between malformations and deformities in the strict sense of the terms. DeMyer (Chapter 18 in this volume), for example, points out that anophthalmia might result from a number of different mechanisms: the inductive influences of the prechordal mesoderm might fail or the diencephalic floor might be unable to respond to the inductive stimulus (malformation); if induction does occur, selective cell death of neural tissue, either from exogenous or genetic causes, might result in regression of an already well-formed eye (deformity).

From any point of view, therefore, these late occurring malformations and deformities are as real and catastrophic as those of early origin, present the same problems to both the patient and the clinician, and contribute to the load of malformations in individuals, families and populations.

Malformations present at birth or discovered during the neonatal period are referred to as *congenital* malformations. Yet, the neonatal period is a very poor time, indeed, to observe and record malformations. To begin with, development is not entirely complete at birth. The CNS of the neonate would qualify as congenital malformation: myelination has not yet taken place, the cortex is not fully developed, and the cerebellum is quite small. Often, though the malformation mechanism may have begun in embryonic or fetal life, many malformations of the nervous system, and of other systems as well (patent ductus arteriosus, pyloric stenosis), do not become manifest until days, weeks or months after birth. These escape diagnosis during the neonatal period.

In the prospective Collaborative Perinatal Project involving 53,257 pregnancies, Myrianthopoulos and Chung (1974) extended the period of observation of malformations through the first year of life. They found that only about one-third of malformations observed through the first year of life was recognized at birth. This finding is neither new nor unique. McIntosh et al. (1954) and Mellin (1963) in the Fetal Life Study from New York City, found that of 465 malformations observed among 386 liveborn infants, 43.2% were detected at birth, 38.7% at six months and the rest after one year of age. And Neel (1958), in his study of major congenital defects in Japanese infants, found that on reexamination of approximately one-fourth of the original infant population at nine months, 1.75% of them had malformations not detected at birth, a proportion higher than that of infants who had malformations at birth, 1.37%. Similar observations were reported by McKeown and Record (1960) and Kleinman et al. (1962).

Another factor which complicates the accurate detection of malformations at birth is the uncertainty in diagnosis. Malformations of the nervous system are especially susceptible to this uncertainty. While the diagnosis of anencephaly, for example, can readily be made at birth, a child may appear early in life to be microcephalic or hydrocephalic but a definite diagnosis cannot be made. In the Collaborative Perinatal Project all observations of malformations and other conditions at birth were regarded as 'definite' or 'suspect'. The

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Project children were given several thorough pediatric examinations before they were discharged from the hospital after birth, a pediatric examination at four months, and a pediatric-neurologic examination at one year of age. By that time most suspect conditions either became definite or disappeared.

Table 1 shows several CNS malformations in the Collaborative Perinatal Project, which occurred with sufficient frequency to illustrate the point. Of the nine malformations, only anencephaly could be definitely diagnosed at birth in each case. A definite diagnosis of microcephaly, hydrocephaly and craniosynostosis could be made in less than one-third of cases at birth, though most of the suspect cases turned out definite by one year. All cases of abnormal separation of sutures and encephalocele remained definite at one year while their corresponding suspect diagnoses had to be discarded. The four suspect diagnoses for spina bifida became definite at one year but nine more were recognized during that period. Pilonidal sinus provides a good example of the diagnostic confusion. And Down syndrome, whose clinical picture is fairly well defined and recognized, was missed as a definite diagnosis at birth almost 25% of the time.

Confronted with all these difficulties we may well join McKeown and Record (1960) in asking whether anything is gained by attempting to define malformations. As these authors point out, definitions are useful in malformation studies, to make decisions as to what to include, time of observation, level of pathology, severity, classification, enumeration, and comparison of incidences of malformations.

TABLE 1

Suspect and definite malformations of the nervous system at birth and during the first year of life. (Data from the Collaborative Perinatal Project.)

	At birth		During first year of life
	suspect	definite	
Anencephaly	0	33	33
Microcephaly	84	12	85
Hydrocephaly	105	36	75
Craniosynostosis	26	9	28
Abnormal separation of sutures	197	89	89
Encephalocele	3	9	9
Meningomyelocele/meningocele	4	26	39
Pilonidal sinus	98	62	122
Down syndrome	41	45	57

What then, if any definition shall we follow in compiling and presenting malformations of the nervous system in a comprehensive compendium? We prefer not to be bound by restrictions. The clinician who is confronted with a grossly malformed patient or one with suspected abnormalities of the nervous system, is not much interested in definitions. He wants to know as much as possible about what went wrong, where, when and how and what can be done about it. We will consider, then, under the general term 'malformation' any congenital and developmental deviation from normality, gross or microscopic, manifesting at birth or at any time later, if there is reasonable certainty that the malformation process began during the developmental continuum of form and function, and exemplifies one of the accepted malformation patterns: agenesis, aplasia, hypoplasia, dysplasia, and deformity.

Agenesis means the absence of an organ, which usually results from failure of appearance of the organ primordium in embryonic development. Ageneses are rare malformations and most of them are probably aplasias (see below). It is difficult to distinguish between agenesis and aplasia without the benefit of very careful dissection and histologic preparation.

Aplasia is the lack of development of an organ or tissue even though the primordium has appeared.

Hypoplasia refers to incomplete development of an organ so that it fails to reach maturity. It must be stressed that hypoplasias, like hyperplasias have normal morphology; the change is only in size.

Dysplasia is a pathologic term denoting an abnormality of tissue, as distinguished from an abnormality of an organ. Vascular malformations, neoplasms and heterotopias would, in the strict sense, be considered dysplasias.

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Deformity has already been defined and discussed.

Among malformations, we will also include metabolic disorders and malformation syndromes not primarily of the nervous system, if they have associated nervous system malformations.

MAJOR AND MINOR MALFORMATIONS

Malformations vary greatly in severity and are usually divided into *major* and *minor*, on the basis of their prognosis, cosmetic significance, and other criteria for which there is no general agreement. There can be no dispute, of course, that anencephaly, a lethal condition, is a major malformation; and most workers will accept that café-au-lait spots or preauricular pits and tags are minor malformations, though this might be a premature assumption, as we shall see later. But most malformations fall in an area of varying uncertainty between these seemingly uncontroversial extremes and cannot be unquestionably assigned to the one or the other group. The search for adequate criteria on which to establish the boundaries of major and minor malformations has been unsuccessful, frustrating and futile, as a few examples of sincere efforts in the literature will show.

In a study of congenital malformations in Wisconsin, Marden et al. (1964) defined a major malformation as one which has an adverse effect on either the function or social acceptability of the individual, and a minor malformation as one which is neither of medical nor cosmetic consequence. Nelson and Forfar (1969) in a study from Edinburgh, considered a major malformation one which is severe enough to cause death or significant handicap, and as minor malformation one which is unlikely to prove a serious hindrance to normal life or to achievement of normal life expectancy. Both definitions are too general and, except for the criterion of death, leave the choice open to the investigator as to what is of medical or cosmetic significance, or a serious hindrance to normal life.

Hook and Petry (1970) in a study from New York State, confined themselves to minor malformations which they defined as anatomic variants which occur at low frequency in the normal population and, as distinguished from major malformations, have no clinical or cosmetic significance per se. The criterion of low frequency is difficult to interpret. Malformations generally accepted as minor, such as supernumerary nipples, café-au-lait spots and polydactyly vary in frequency among racial groups and occur with very high frequencies among Negroes (Woclf and Myrianthopoulos 1973; Myrianthopoulos and Chung 1974). Are these malformations to be considered as minor in some populations but not in others?

Besides, café-au-lait spots, polydactyly, deformed ear pinnas and earpits, and a host of other seemingly innocuous deviations from normality may be omens of something more catastrophic. One café-au-lait spot may be ignored as trivial, but many may indicate multiple neurofibromatosis (Crowe et al. 1956). A sixth finger is usually considered as an easily correctible cosmetic nuisance but it may be a serious prognostic sign of the Laurence–Moon–Biedl syndrome. Malformed ear pinnae, and ear pits are often associated with other malformations and may be manifestations of serious malformation syndromes such as branchio-oto-renal dysplasia (Pinsky 1974; Melnick et al. 1975).

Myrianthopoulos and Chung (1974) in their prospective study of congenital malformations which occurred in the Collaborative Perinatal Project, considered and ultimately discarded a number of similar criteria. One proposed criterion, that a malformation would be considered major if it posed threat to life, soon proved inadequate, for even such admittedly significant malformations as absence of a whole limb or achondroplasia are not threatening to life. Another proposed criterion that if a malformation required surgery it would be considered major, also proved inadequate, for such admittedly minor malformations as preauricular skin tags and pigmented nevi may require surgical removal. The authors admitted that in that study, though they followed certain guidelines, their decision to assign a malformation to the major or minor category was, in the last analysis, arbitrary and was based on expert advice as well as their own experience and intuition rather than on any one criterion or set of criteria. As it turned out, these authors classified all of their nervous system malformations as major,

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with the exception of pilonidal sinus which they classified as minor. Yet pilonidal sinus is prone to infections which can present complications and have serious consequences for the patient.

Myrianthopoulos and Chung emphasized a point worth repeating. The a priori assignment of certain malformations to the minor group serves only the purpose of defining the malformations and describing their epidemiologic characteristics. But the most important consideration from the point of view of the individual's personal welfare, and of public health in general, would be to determine their clinical significance, i.e., to establish which minor malformations are worth detecting and why, and which ones can be ignored or considered as normal variants.

In keeping with this philosophy, no attempt at classification according to severity is made in these volumes. Rather, in this context, the emphasis is placed on the clinical significance of each nervous system malformation, its immediate and long-term effect on the health status and welfare of the patient, and the prospects for good management and treatment.

MULTIPLE MALFORMATIONS

Malformations, particularly those of or involving the nervous system, are often multiple. They are found in association with other nervous system malformations, or as a part of a multiple malformation complex involving other systems as well, which may or may not represent a syndrome. Table 2 shows the most frequent CNS malformations observed in the Collaborative Perinatal Project, which occurred in single or multiple form. All of them occurred as multiple malformations, most of them more often multiple than single, the proportion of multiple ranging from 25–89%.

Both genetic and environmental factors can lead to multiple malformations. As Warkany (1971) put it, 'Abnormal genes, chromosomes and environmental factors show little respect for the limits of organs as we know them in postnatal life'.

The most common genetic cause of multiple malformations is pleiotropy. The term means multiple effects, or multiple phenotypic features

TABLE 2

Malformations of the nervous system occurring as single and multiple. (Data from the Collaborative Perinatal Project.)

	Single	Multiple	% Multiple
Anencephaly	11	22	66.7
Microcephaly	39	46	54.1
Hydrocephaly	25	50	66.7
Macrocephaly	30	12	28.6
Craniosynostosis	16	12	42.9
Abnormal separation of sutures	49	40	44.9
Encephalocele	1	8	88.9
Meningomyelocele/meningocele	5	34	87.2
Pilonidal sinus	92	30	24.6

of one etiologic factor, in this case a single gene locus. These multiple phenotypic features constitute a true syndrome, such as the Laurence–Moon–Biedl syndrome, the cerebro-hepato-renal syndrome, the Seckel syndrome. Linkage, i.e. close situation of genes for different malformation phenotypes on the same chromosome, may also result in multiple malformations, though the association of these malformations will not be permanent, because of crossing-over.

Chromosomal aberrations are, of course, notorious for producing multiple malformations. In this case, however, it is almost certain that the multiple malformations are a result of the independent or collective action of several genetic components of the aberrant chromosome.

Environmental factors, acting early in embryogenesis, such as rubella infection, often lead to widespread pathologic changes and multiple malformations in several body systems and organs. Presumably, such factors act destructively on several organ system primordia. By far the majority of multiple malformations, however, represent chance associations or hitherto unrecognized syndromes.

The identification, definition and classification of multiple malformations has occupied the attention – and imagination – first of clinical teratologists, and more recently of the teratologic taxonomists who sought to create some order out of the multitude of combinations in which mal-

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