Textbook of

CHILD NEUROLOGY

second edition

JOHN H. MENKES

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CHILD NEUROLOGY

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Textbook of

CHILD NEUROLOGY

To My Teachers:

B.G.B.

S.S.G.

A.S.N.

S.C.

D.B.C.

(There was)

"a time when theses in medicine could still be beautifully literary, since ignorance about diseases and the human body still required that medicine be an art."

Kurt Vonnegut, Jr.

Preface

A great number of alterations in the second edition of this book reflect the advent of computer assisted tomography, which has revolutionized neurologic diagnosis and management in all age groups. In pediatric neurology this is particularly so for the infant with hydrocephalus, the head-injured child, and the brain tumor suspect. On the other hand, there is now a tendency for the routine, mindless application of this diagnostic tool, and inevitably there is much talk of reducing neurology to a series of totally computerized diagnostic studies. Such a proposed simplification of neurology is worrisome to one who still believes that a careful history and physical examination continue to take precedence in the evaluation of the child with a neurologic disorder.

Other advances have also left their mark on the new edition. One by one, the metabolic basis for the hereditary degenerative diseases is becoming clear. Friedreich's ataxia, for instance, is now believed to be associated with a disorder in pyruvate metabolism, adrenoleukodystrophy is probably due to a faulty handling of the very long-chain fatty acids, and Kinky Hair disease, like Wilson's disease, has turned out to be a disorder of copper metabolism.

Some of the neurologic diseases are no longer as common as they were when the first edition appeared in print. Spastic diplegia, for instance, is an entity that soon may not be with us, promising to join the ranks of diseases such as neurosyphilis, which disappeared without their pathogenesis becoming fully understood. Tay-Sachs disease is another entity that is becoming a rarity thanks to efficient screening programs for the heterozygote, and the in utero detection of the homozygous fetus.

The advent of sodium valproate, belatedly approved for use in the United States in 1978, may well change the management of epileptic patients, particularly those with minor motor attacks, and may allow physicians to control their seizures without undue sedation.

Other areas, notably the muscle diseases and neuroimmunology, have also seen considerable progress, for instance in our understanding of the pathogenesis of muscular dystrophy and multiple sclerosis. As yet, however, this advance has not been translatable into successful therapy for these diseases.

As happened in the preparation of the first edition, the author enlisted the formal and informal assistance of a number of colleagues. Special indebtedness must be set down for the following:

Dr. Victor Dubowitz, Department of Paediatrics, Hammersmith Hospital, London.

Dr. George W. Ellison, Department of Neurology, UCLA School of Medicine.

Dr. Stephen Feig, Department of Pediatrics, UCLA School of Medicine.

Dr. Christian Herrmann, Department of Neurology, UCLA School of Medicine.

Dr. H. E. Neville, Department of Neurology, University of Colorado School of Medicine.

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Preface to the First Edition

Even in a textbook, prefaces are written not to be read but rather to blunt inevitable criticisms. One must therefore first ask, why, in view of the existence of several first-rate pediatric neurology texts, was this book ever written. The main excuse for becoming involved in such an undertaking, and for imposing another book upon an already overwhelmed medical audience, is the hope of being able to offer a new viewpoint of the field. More than any other branch of clinical neurology, pediatric neurology has felt the impact of the many recent advances in the neurosciences. Their magnitude becomes evident when the neurologic literature of the last century is read. At that time clinical descriptions achieved a degree of clarity and conciseness, which has not been improved upon, and which at present is only rarely equalled. Yet the reader who finds the explanation of Tay-Sachs disease* offered during the last years of the nineteenth century must experience a sense of achievement at the great strides made during a relatively brief historical period. However, at the same time, one cannot but wonder how many of our "explanations," accepted and taught today, will make as little sense fifty years hence.

It is the aim of this text to incorporate some of the knowledge derived from the basic neurologic sciences into the clinical evaluation and management of the child with neurologic disease. Obviously this can only be done to a limited extent. For some conditions the basic sciences have not yet offered any help, while for others, available experimental data only provide tangential information. Even when biochemical or physiologic information is pertinent to the conditions under discussion, their full presentation has been avoided, for to do so with any degree of completeness would require an extensive review of several scientific disciplines, which would go far beyond the intent of the text. The author and his colleagues have therefore chosen to review only aspects of the neurologic sciences with immediate clinical impact, and to refer the reader to the literature for some of the remaining information. They have also deemed it appropriate *not* to include a section on the neurologic examination of children. This subject is extremely well presented by R. S. Paine and T. E. Oppe,

*Namely, "an inherited weakness of the central nervous system, especially of the ganglion cells, and a premature degeneration due to exhaustion caused by this."

*The Neurologic Examination of Children,** a work everyone seriously interested in pediatric neurology should read.

In covering the field, extensive use of literature references has been made. These generally serve one or more of the following purposes:

(1) A classic or early description of the condition.

(2) Background information pertaining to the relevant neurologic sciences.

(3) A current review of the condition.

(4) In the case of some of the rarer clinical entities, the presentation of several key references was preferred to a brief and obviously inadequate summary.

It is hoped that this approach will serve to keep the text reasonably compact, yet allow it to be used as a guide for further reading.

The author is indebted to a number of colleagues for their critical manuscript reviews and suggestions:

Dr. John M. Adams, Department of Pediatrics, UCLA.

Dr. Barbara F. Crandall, Division of Genetics, UCLA.

Dr. Theodore L. Munsat, Department of Neurology, Tufts University.

Dr. Robert C. Neerhout, Department of Pediatrics, University of Oregon.

Dr. Gerhard Nellhaus, Napa State Hospital, Napa, California.

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*London, Wm. Heinemann, 1966.

Contents

1

Metabolic Diseases of the Nervous System

Although the diseases considered in this chapter are various in both their clinical and pathologic aspects, their genetic transmission implies that they are directly or indirectly the results of inborn enzymatic defects.

Over the past 20 years the number of disorders to which we are able to assign a known enzymatic lesion has increased strikingly. Even so, they are relatively uncommon, and their importance lies, in part, in the insight they offer into the normal development and function of the human nervous system. In some of the metabolic disorders, such as sucrosuria,[1] cystathioninuria,[2] or hyperprolinemia,[3] Types I and II, the association of a neurologic disturbance may be fortuitous and merely the result of subjecting retarded children, a highly selected group, to biochemical examination. A survey of the normal adult population for the presence of inborn errors of metabolism is needed to determine which of these conditions represent harmless metabolic variants.

For practical purposes, the metabolic disorders are divided into 9 groups:

1. Disorders of amino acid metabolism associated with neurologic symptoms
2. Disorders in amino acid transport
3. Disorders of carbohydrate metabolism
4. The mucopolysaccharidoses
5. The mucolipidoses and disorders in glycoprotein metabolism
6. Disorders manifested by intermittent metabolic acidosis (organic-acidurias)
7. Disorders of lipid metabolism
8. Disorders of metal metabolism
9. Disorders of purine metabolism

DISORDERS OF AMINO ACID METABOLISM

Phenylketonuria

Phenylketonuria is an inborn error of metabolism manifested by the inability of the body to convert phenylalanine to tyrosine; untreated, it produces a clinical picture highlighted by mental retarda-

tion, seizures, and imperfect hair pigmentation.

In 1934[4] Følling first called attention to the condition in a report of 10 mental defectives who excreted large amounts of phenylpyruvic acid. The disease has been found in all parts of the world, although it is rare in Negroes or in Jews of European descent. Its frequency in the general population of the United States, as determined by screening programs, is approximately 1 in 14,000.[5] As determined by surveys such as that of Jervis,[6] the frequency of the condition among mentally defective individuals is approximately 1 in 200.

The genetics of phenylketonuria have been well-studied. Jervis[6] found that of 1,094 siblings of phenylketonurics, 433 (40%) were affected. When statistically corrected for uncounted families of heterozygous parents with only normal children, the percentage of affected children of heterozygous parents becomes 27%, a close approximation to the 25% expected for an autosomal recessive condition.

BIOCHEMICAL PATHOLOGY. Jervis,[7] Udenfriend and Bessman,[8] and Wallace et al.[9] proved the metabolic defect responsible for phenylketonuria to be an inability to convert phenylalanine to tyrosine (Fig. 1–1).

In man phenylalanine is an essential dietary constituent and is necessary for protein synthesis. In mammals, the conversion of phenylalanine to tyrosine is irreversible, and the latter cannot replace phenylalanine in a minimal diet. Kaufman and Levenberg (and subsequent work emanating from Kaufman's laboratory) revealed that the hydroxylation of phenylalanine is a complex reaction requiring at least 2 enzymes and numerous nonprotein components.[10] Phenylalanine hydroxylase, a heat-labile enzyme, is normally found in liver, kidney, and pancreas, but not in brain or skin fibroblasts.[11,12] The enzyme has a molecular

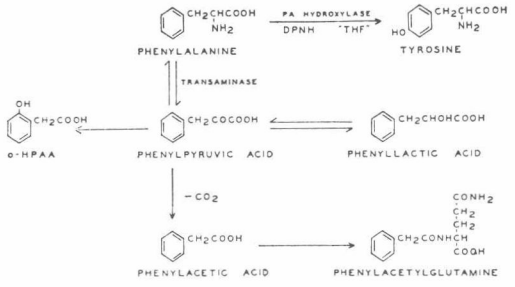

Fig. 1–1. Phenylalanine metabolism. The hydroxylation of phenylalanine to tyrosine is blocked in phenylketonuria. All the intermediary metabolites depicted above have been found in urine or blood.

weight of 108,000 and contains iron and possibly copper. In liver it has been isolated in the form of 3 isoenzymes. About half of normal adults have all 3 isoenzymes; the remainder have 2 isoenzymes.[13] As yet dispute still exists whether these represent artifacts incurred in the course of isolation.[14] In vivo regulation of enzyme activity may be accomplished by its phosphorylation, which adds 4 moles of inorganic phosphate and increases hydroxylase activity. Dephosphorylation by means of a phenylalanine hydroxylase phosphatase reduces, but does not abolish, enzyme activity.[15] In addition, a hydroxylase-stimulating protein plays a role in the conversion of phenylalanine to tyrosine. This macromolecule is an enzyme that catalyzes the conversion of a phenylalanine intermediate, which is released in the course of the hydroxylation.[16] In phenylketonuria, phenylalanine hydroxylase is structurally altered so that its activity is completely, or nearly completely, abolished.[17]

Dihydropteridine reductase, a heat-stable enzyme, is present in normal amounts in classic phenylketonuria, but is absent or defective in at least one of the more recently discovered variants. The hydroxylation of phenylalanine also re-

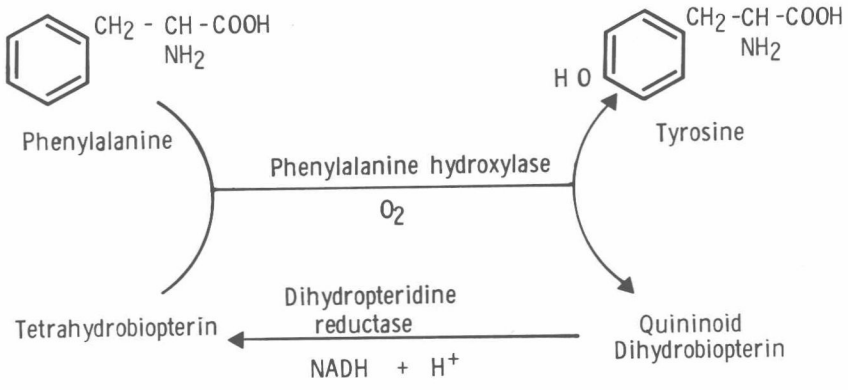

Fig. 1–2. Mechanism of phenylalanine hydroxylation. Phenylalanine hydroxylase is deficient in phenylketonuria. Dihydropteridine reductase reconverts the quininoid or oxidized form of the pteridine to tetrahydropteridine.

quires oxygen and dihydrobiopterin.[16] The latter is converted to tetrahydrobiopterin in a reaction catalyzed by dihydrofolate reductase and a reduced pyridine nucleotide (NADPH).[17] Tetrahydrobiopterin participates directly in the hydroxylation of phenylalanine and is converted to its quininoid form.

The phenylalanine hydroxylation system, as first proposed by Kaufman,[18] is set forth in Figure 1–2. As expected from this mechanism, amethopterin or other folic acid antagonists inhibit the conversion of phenylalanine to tyrosine in both animals and humans.[19] Owing to a partial deficiency of the cofactor, and possibly also of dihydropteridine reductase, the phenylalanine hydroxylating system is less active in human fetal liver than it is in the adult.[20,21] Phenylalanine hydroxylation reaches adult levels by the third to the twelfth day of postnatal life, but until then serum phenylalanine levels are somewhat higher than those of older infants or adults (up to 7.5 mg/dl contrasted with a normal range of 1.0 to 2.5 mg/dl).[22] This transitory defect in phenylalanine hydroxylation is even more pronounced in premature infants.[23]

Phenylketonuric children are born with only slightly elevated phenylalanine blood levels, but because of the absence of phenylalanine hydroxylase activity, the amino acid derived from food proteins accumulates in serum and cerebrospinal fluid and is excreted in large quantities. In lieu of the normal degradative pathway, phenylalanine is converted to phenylpyruvic acid, phenylacetic acid, and phenylacetylglutamine (see Fig. 1–1).

The transamination of phenylalanine to phenylpyruvic acid is sometimes deficient for the first few days of life, and the age when phenylpyruvic acid may be first detected varies from 2 to 34 days. From the first week of life, o-hydroxyphenylacetic acid is also excreted in large amounts.[24] This derivative is formed in liver and kidney from phenylpyruvic acid, the conversion requiring ascorbic acid and an enzyme related to p-hydroxyphenylpyruvic acid oxidase.[25,26]

Liver contains sufficient phenylpyruvic acid hydroxylase to convert all of the phenylpyruvic acid formed by transamination of phenylalanine to o-hydroxyphenylacetic acid, and any phenylpyruvic acid in urine is probably formed in muscle, brain, or heart.[27]

Table 1–1.
Concentration of some phenylalanine metabolites in phenylketonuria.

	PHENYLKETONURICS		NORMALS	
	SERUM	URINE	SERUM	URINE
Phenylalanine	15–100 mg/dl	0.4 g/24 hr	0.84–2.64 mg/dl	18 mg/24 hr
Phenylpyruvic acid	0.1–1.68 mg/dl	0.7–2.8 g/24 hr	approx. 0	approx. 0
o-Hydroxyphenylacetic acid	—	0.1–0.4 g/24 hr	—	<1 mg/24 hr
Phenylacetylglutamine	—	0.3–2.4 g/24 hr	—	250–500 mg/24 hr

Compiled from Jervis,[28] La Du and Michael,[29] Armstrong et al.,[26] and Partington and Vickery.[31]

The abnormal concentration of metabolites in serum and urine is depicted in Table 1–1.

In addition to the disruption of phenylalanine metabolism, tryptophan and tyrosine also are handled abnormally. Large amounts of indolyl-3-lactic acid, indolyl-3-acetic acid, indolyl-3-pyruvic acid, and indican have been found in the urine.[32,33,34] Conversely, the levels of 5-hydroxytryptamine (serotonin) in serum and of 5-hydroxyindolylacetic acid in urine are decreased.[35]

In vitro studies and work on phenylalanine loaded rats suggest that this alteration in 5-hydroxyindole production is the result of an inhibition of 5-hydroxytryptamine synthesis at as many as 3 different sites.[36]

Intestinal transport of L-tryptophan and tyrosine is impaired in phenylketonuria, and fecal tryptophan and tyrosine content is increased. These abnormalities are reversed following dietary correction of the plasma phenylalanine levels.[37]

Miyamoto and Fitzpatrick have suggested that a similar interference may occur in the oxidation of tyrosine to dihydroxyphenylalanine (DOPA), a melanin precursor, and may be responsible for the deficiency of hair and skin pigment in phenylketonuric individuals.[38]

PATHOLOGIC ANATOMY. The alterations within the brain are nonspecific and diffuse. They involve both gray and white matter, and probably progress in severity with increasing age. They are of 3 types:

1. Interference with the normal maturation of the central nervous system. Brain growth is reduced, and on microscopic examination one observes impaired cortical layering, delayed outward migration of neuroblasts, and heterotopic gray matter.[39,40] These changes suggest a period of abnormal brain development during the last trimester of gestation (Fig. 1–3).

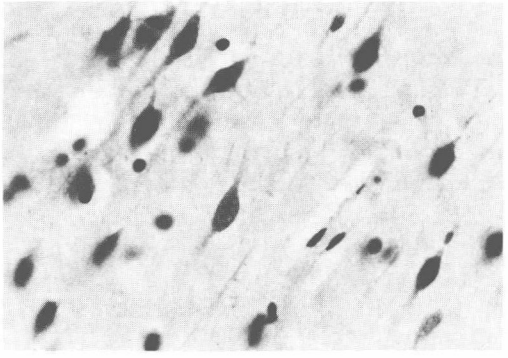

Fig. 1–3. Phenylketonuria. Cresyl violet stained section showing spindle-shaped immature neuron in the center of the field. These cytoarchitectural abnormalities are nonspecific. Together with the convolutional abnormalities they indicate a developmental arrest. × 350. (Courtesy of Dr. N. Malamud, Langley Porter Neuropsychiatric Institute, San Francisco, California.)

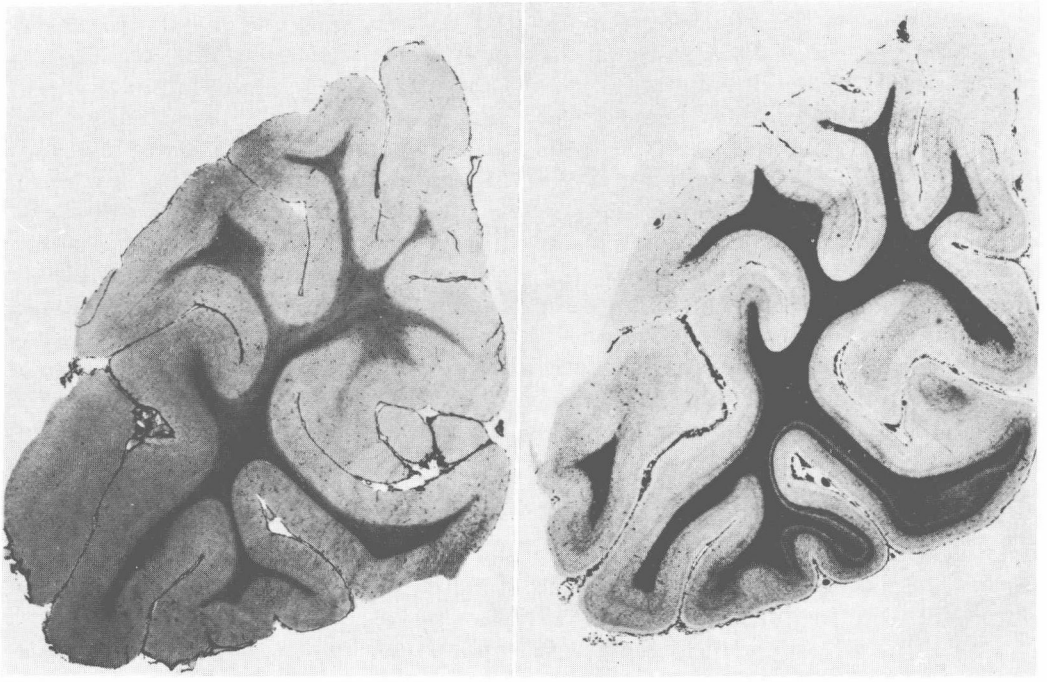

Fig. 1–4. Phenylketonuria, occipital lobe. Stained by the Heidenhain method for myelin on the right and the Holzer method for fibrous gliosis on the left. The dark hue of the white matter on the left indicates the presence of fibrous gliosis. The picture on the right shows normally staining myelin. × 2.5. (Courtesy of Dr. L. Crome, Queen Mary's Hospital for Children, Carshalton, Surrey, England.)

2. Defective myelination. This may be generalized or limited to those areas where one may expect postnatal myelin deposition. Except in some older patients, products of myelin degeneration are unusual.[41] Generally one observes a relative pallor of myelin that may be accompanied by a mild degree of gliosis (Fig. 1–4) and irregular areas of vacuolation (status spongiosus). The latter are usually seen in central white matter of the cerebral hemispheres and in the cerebellum. Lacking electron microscopic examinations it is not known whether the cysts represent dilatation of the glial cells or of the myelin sheath.

3. Pigmentation of the substantia nigra and locus caeruleus is diminished or absent. As those areas are normally pigmented in albinos and as tyrosinase activity cannot be demonstrated in normal neurons within the substantia nigra,[42] this is not a result of tyrosinase inhibition by phenylalanine or its derivatives. Rather, neuromelanogenesis in the phenylketonuric patient must be interrupted at some other metabolic point, such as the metal-catalyzed pseudoperoxidation of dopamine derivatives probably responsible for the melanization of substantia nigra lipofuscin.[42]

The association of ulegyria or micropolygyria with phenylketonuria has been considered to be coincidental or the result of prolonged seizures.[40]

CLINICAL MANIFESTATIONS. Phenylketonuric infants appear normal at birth. During the first 2 months of life, vomiting

(which may even be projectile) and irritability are frequent. By 4 to 9 months delayed intellectual development becomes apparent.[43] In the classic case, mental retardation may be severe, precluding speech and toilet training. Children in this category have an intelligence quotient below 50. Seizures, common in the more severely retarded, usually start before 18 months of age and may cease spontaneously. During infancy they may take the form of infantile spasms, later changing into grand mal attacks.

The typical child is blond and blue-eyed with normal and often pleasant features. The skin is rough and dry, sometimes with eczema. A peculiar musty odor, attributable to phenylacetic acid, may suggest the diagnosis. Significant neurologic abnormalities are rare. Microcephaly may be present as well as a mild increase in muscle tone, particularly in the lower extremities. A fine, irregular tremor of the outstretched hands is seen in about one-third of subjects. The plantar response is often variable or extensor.

Older children are quite restless and hyperactive; they are prone to repetitive movements of body and hands. We have observed intellectual deterioration in several of our patients—the outcome of the institutional environment or a function of the natural history of the disease.

A variety of electroencephalographic abnormalities has been found, but hypsarrhythmic patterns, recorded even in the absence of seizures, and single and multiple foci of spike and polyspike discharges are the most common.[44,45]

Untreated phenylketonuria is not invariably accompanied by intellectual deficit. About 1 to 4% of patients with untreated classic phenylketonuria achieve intelligence quotients of 80 or above.[46,47]

On theoretic grounds individuals heterozygous for phenylketonuria should have a partial deficiency of phenylalanine hydroxylase and therefore some impairment in their ability to metabolize phenylalanine. As yet no completely satisfactory method exists for ascertaining the heterozygote. According to Perry,[48] fasting phenylalanine levels and phenylalanine-tyrosine ratios determined spectrophotometrically tend to be higher in heterozygotes than in normal subjects. Criteria for diagnosing a heterozygote are: a fasting serum phenylalanine level of 1.80 mg/dl or higher and a phenylalanine-tyrosine ratio greater than 1.60. Griffin and Elsas have used midday semifasting serum phenylalanine and tyrosine determinations to calculate a $(\text{Phenylalanine})^2/(\text{Tyrosine})$ ratio. In their series no overlap occurred between heterozygotes and controls.[49] Despite these carefully performed studies, it is doubtful whether in practice the genotype of a given subject can be ascertained with certainty by amino acid levels or by his response to a phenylalanine load. Phenylalanine hydroxylase has not been detected in skin fibroblast cultures derived from normal individuals, and therefore this tissue cannot be used in the detection of the heterozygote. An antenatal diagnosis of the disease also has not been possible.

Heterozygous mothers may have abnormal plasma phenylalanine levels during the latter part of pregnancy and following delivery. In at least one instance, a plasma phenylalanine value of 13.0 mg/dl (upper limit of normal: 2.5 mg/dl) was recorded at 32 weeks' gestation.[50]

Although the incidence of spontaneous abortions is high, a number of phenylketonuric women have had children. Over 90% of the offspring, although heterozygotes, showed pre- and postnatal growth retardation, microcephaly and severe intellectual delay. In 25% there were major congenital malformations. Because maternal plasma phenylalanine concentration is about half that of the fetus, it seems likely that the high amino acid level in the pregnant phenylketonuric mother may damage the fetus.[46,51]

Since a diet restricted in phenylalanine