NUTRITIONAL TREATMENT OF INBORN ERRORS OF METABOLISM

Essay

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By

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A C K N O W L E D G E M E N T

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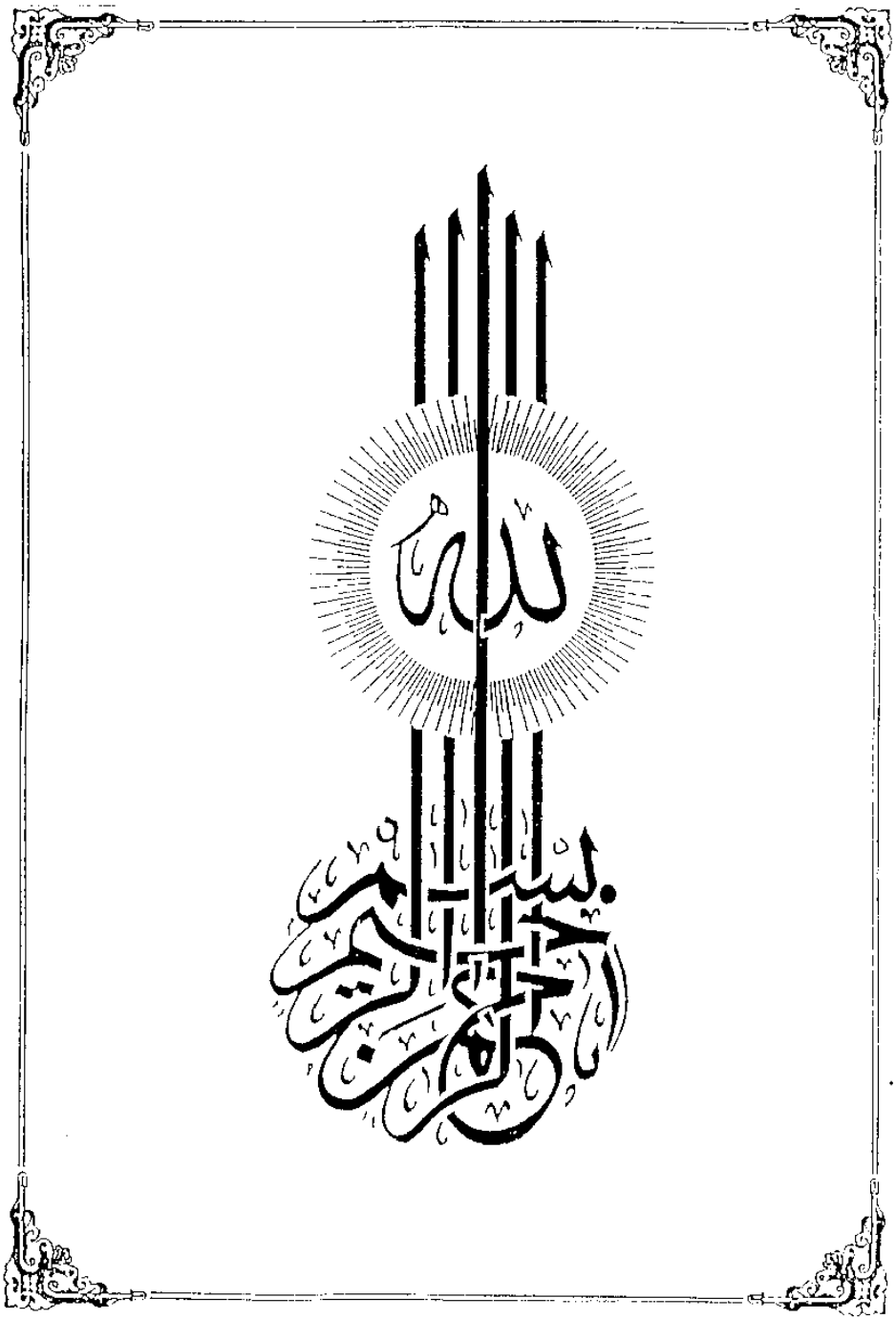

C O N T E N T S

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Several other modes of therapy of genetic diseases are readly available. For review of strategies of therapy of genetic diseases see Shapiro (1983).

It is inherent in the medical genetics that virtually all disease results from an interaction of environmental and hereditary factors (Stern, 1973). Alteration of the genetic constitution of individuals has not been acheived yet. On the other hand, we can control the environmental factors in many disorders. Thus, while few would dispute that phenylketonuria is a genetic illness, it is only of pathological consequence in the context of an environment which provides dietary phenylalanine in excess of the subject's ability to metabolize it, and through appropriate environmental intervention, the adverse effect of the mutant gene can be lessened.

The goal of nutritioal therapy can perhaps be codified as an attempt to create an equilibrium between inherited factors & environmental influences by alteration of the diet to allow the individual to live as full and healthy life as possible.

GENERAL PRINCIPLES OF NUTRITIONAL THERAPY

The goals of diet therapy are: (1) preservation of the integrity of the CNS; (2) permittion of normal growth (3) normalization of affected biochemical parameters (Cohn and Roth, 1983).

Several therapeutic modalities of nutritional therapy can be applied in different metabolic disorders. Choice of the effective modality is dictated by the nature of the disease and its biochemical consequences.

Some situations permit a relatively simple form of therapy: simple elimination of the offending dietary component or the substrate of defective enzyme. This is feasible in cases in which this compound is non essential i.e. can be endogenously synthesized. The metabolic relationship of glucose with fructose and galactose allows the elimination of any of these sugars in cases in which metabolic abnormality of either of galactose or fructose exists. (Martin et al., 1981).

In other situations complete elimination of the offending substrate may be even more deleterious than supplying it in normal quantities; in such conditions Partial elimination of offending dietary component is necessary.

The most eminent example of this type of nutritional therapy is phenylketonuria where phenylalanine should be supplied in amounts which prevent the occurance of the d deleterious hypophenylalaninemia (Page, 19)

Another approach is the supply of a non toxic analogue of the parent compound; this approach can be useful in a number of disorders of urea cycle where reduction of dietary nitrogen loading by feeding alpha-keto analogues of the amino acids has lowered the plasma ammonia level. Unfortunately the biochemical efficacy of this therapy has not resulted in clinical response of equal measure (Thoene et al., 1975).

Another option is the administration of a detoxifying dietary constituent. The use of glycine in isovaleric acidemia where glycine forms isovalerylglycine leads to amelioration of the toxic effect of isovaleric acid (Roe et al, 1985).

The product of the defective reaction can be supplied in diet in few disorders. An example of this is the administration of arginine in citruillinemia which provides large amounts of ornithine through the action of arginase (Scott, 1983).

Certain disorders involve cofactor dependant enzyme pathways, a subgroup of which are "vitamin responsive disorders". There are four mechanisms of vitamin responsiveness of inborn errors of metabolism.

1) Defective biosynthesis or transport of coenzyme:

With the exception of biotin and ascorbic acid, specific steps are required for the biosynthesis of all coenzymes from their parent vitamins (Scriver, 1973). A partial block of the pathway of coenzyme synthesis may be overcome by the administration of the precursor vitamin in pharmacologic dose. Vitamin B_{12} is an excellent example of this mechanism of vitamin responiveness.

Several defects in the absorbtion or transport of Vitamin B_{12} can result in megaloblastic anemia which is corrected by pharmacologic doses of the vitamin. In the final stages of B_{12} utilization cobalamin is reduced and ultimately forms both adenosyl and methyl coenzyme. Defects in the pathway of vitamin B_{12} result in methylmalonic aciduria, homocystinuria or both, Figure (1).

2) Defective association of coenzyme with apoenzyme:

Coenzyme must achieve a specific steric relationship

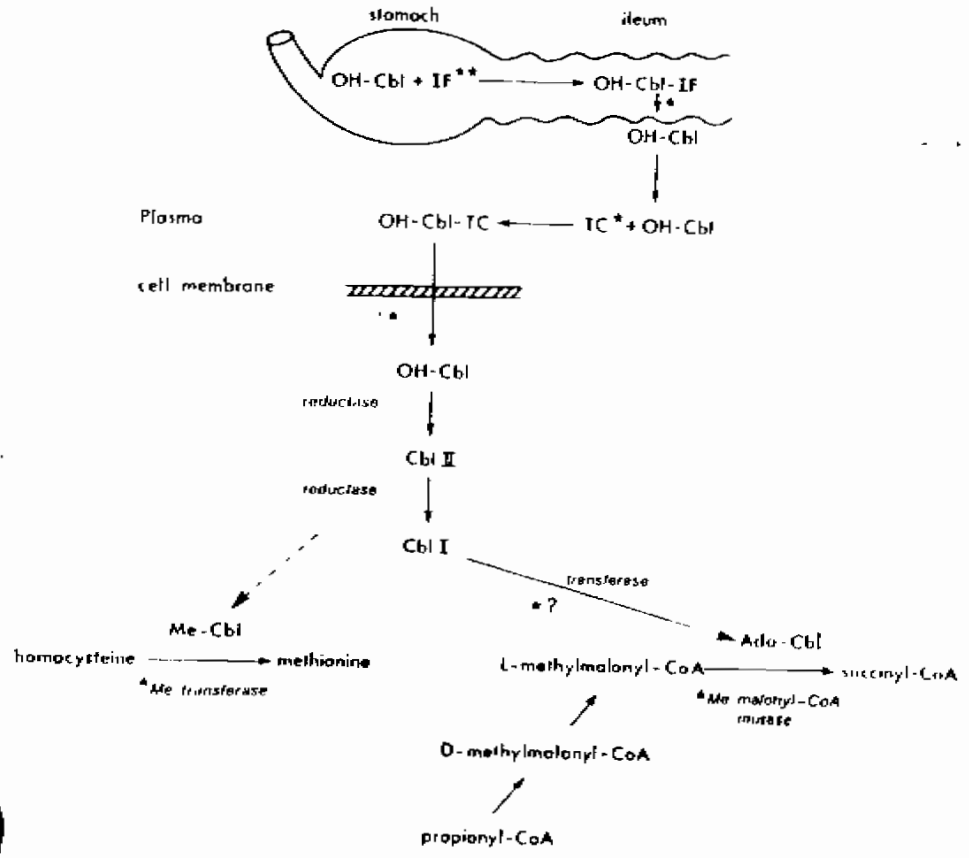

Fig (1) The pathway of Vitamin B_{12} metabolism.

Dietary hydroxycobalamin (OH Cbl) combines with the intrinsic factor (IF) in the stomach. The complex attaches to specific receptor in the ileum and OH Cbl is transported across the intestinal wall into the blood where it binds to transcobalamin (TC) that carries it to cell. Cobalamin is converted to two active forms. One active form 5'acenosyl-cobalamin (Ado Cbl) is a coenzyme for mitochondrial enzyme methylmalonic Co A mutase, inactivity of which results in methyl malonic aciduria. The other active form (Me Cbl) is involved in folate metabolism acting as coenzyme for the cytoplasmic enzyme homocystein methyltetrahydrofolate methyltransferase, inactivation of which results in one form of homocystinuria.

with the apoenzyme to form the holoenzyme which is the active catalytic agent. In some disorders like cystathioninuria the addition of the cofactor, pyridoxine phosphate, in vitro to tissue homogenates restores the deficient enzyme activity within short time due to activation of the available enzyme (Scriver, 1973).

3) Alteration of the cellular concentration of apoenzyme:

The change in enzyme activity may reflect an altered balance between synthesis and degradation of the mutant enzyme particularly if the saturation of the enzyme retards its inactivation. Mudd and his coworkers (1970) examined the mechanism of responsiveness in vivo in homocystinuria; they observed that vitamin therapy diminished homocystine accumulation due to increased hepatic synthase activity from 2 to 4°/°. In the absence of pyridoxine , the 70 kg individual was able to convert no more than 8 millimoles of methionine daily; but when he received pyridoxine, the conversion rate was 16 millimoles per day. Although this increase might look to be a minimal one, it had a significant effect on the dietary tolerance of the individual to methionine. Most student of inborn errors of metabolism find that the difference between less than 2°/° activity and 5°/° activity of enzyme makes a world of difference to the patient with metabolic disorder e.g.

Cofactor	DISORDER	Therapeutic Dose
Biotin	Multiple carboxylase deficiency	10 mg
	Puruvate carboxylase ""	10 mg
	Propionic acidemia	10 mg
Vitamin B_{12}	Methylmalonic aciduria	250-500ug
	Methylmalonic aciduria+ homocystinuria	500 ug
	Interinsic factor deficiency	5 ug
	Transcobalamin II "	100 ug
Ascorbate	Neonatal tyrosinemia	50-100 mg
olate	Megaloblastic anemia due to folate reductase Def.	0.1-0.2 mg
	Homocystinuria + hypo-methioninemia	10 - 20 mg
otinamide	Tryptophanuria	100 mg
	Hartnup disease	50 -200 mg
doxine	Cystathioninuria	100-500 mg
	Homocystinuria	25 -500 mg
	Xanthinurenic aciduria	5 - 10 mg
	Hyperoxaluria	100-500 mg
mine	MSUD	5 - 10 mg
	Pyruvic acidemia	5 - 20 mg
min D	Vitamin dependant rickets	25000 to 50000 I.U.

Table (1) The common cofactor responsive inborn errors of metabolism (Cohn &Roth,1983)

maple syrup urine disease (Scriver et al., 1971).

4) Stimulation of an alternative pathway :

In pyruvate carboxylase deficiency thiamin treatment prevents excessive pyruvate and lactate accumultion. Thiamin is not a coenzyme for carboxylase enzyme. Thiamine acts through a small but significant increase of basal pyruvate dehydrogenase activity in tissues (Pincus et al., 1973) it also stimulates gluconeogeneis via an unknown mechanism (Hommes et al., 1980).

NUTRITIONAL THERAPY OF INDIVIDUAL DISORDERS

An increasing number of inborn errors of metabolism have been reported & teremendous progress in understanding, diagnosing and treating these problems has been made in the last decade. From experience gained in treating the more common disorders especially phenyl ketonuria important lessons have been learnt which apply to other disorders and which should enable us to avoid complications arising from treatment.

In the following chapters, individual inborn errors of metabolism that are responsive to nutritional therapy will be discussed. The more the disorder is common the more the discussion is a detailed one. Rare disorders, which are usually seen once in a life time or even not encountered by most physicians, are mentioned in breif.

Despite the fact that more care has been given to the practical aspect of the commonest inborn errors of metabolism, it should be emphasized that therapy of these diseases should be undertaken only in centers where both laboratory and clinical experience is available.

HYPERPHENYLALANINEMIA

I. Metabolism of Phenylalanine (Phe):

The chemist Folling (1934) first recognised the existande of a disorder of Phe metabolism. The condition was eventually called phenylketonuria or PKU. It is the corner stone of research in clinical and biochemical genetics(Scott, 1983).

It is now recognised that several genetic entities can cause an elevation of Phe. All interfere with conversion of Phe to tyrosine by reducing the activity of Phe hydroxylase. They are referred to collectively as the hyperphenylalaninemia (Hyperphe).

II. The hydroxylase reaction :

The presence of Phe hydroxylase activity in the soluble fraction of the liver extract, the requirement of atmospheric oxygen and NADH and the specificty to L-Phe were first demonstrated by Undenfriend & Cooper (1952). The hydroxylation system was resolved into two protein components by Mitoma (1956). The nexttmajor step came when Kaufman (1976) identified the structure of tetrahydrobiopterin, an obligatory cofactor, and traced its transformation during hydroxylation.

Types of hyperphenylalaninemia :

In the majority of cases Hyper-Phe is the result of decreased phenylalanine hydroxylase enzyme activity. In 1976 Kaufman have shown that the apoenzyme is structurally abnormal in classical PKU . The clinical picture varies according to the residual enzyme activity, table(2)

Several children have been identified with a deficiency of dihydropteridine reductase as a cause of their elevated blood Phe (Kaufman et al., 1975). Such children are believed to be rare and account for no more than 1°/° of patients with PKU (Scott, 1983).

Subsequently, Leeming et al (1976) reported a different defect with somewhat different clinical picture. Additional reports confirmed that this was a new entity which results of a defect in dihydropteridine synthetase enzyme (Bartholome et al., 1977; Kaufman et al., 1978).

Recently Neiderwieser et al. (1982) reported a new enzymatic defect in GTP cyclohydrolas enzyme, the first step in tetrahydrobiopterin synthesis. Two other cases have been reported later on (Dhondt et al., 1985).