NUTRITIONAL MANAGEMENT IN HEREDITARY METABOLIC DISEASE

Thirteen years ago a dietary approach to the therapy of phenylketonuria was proposed, and data on the usefulness as well as the very real limitations of this program have accumulated in the intervening years. At the present time studies on the application of special diets for use in this disease, as well as for many other hereditary metabolic diseases, are in progress. As wider use is made of procedures for detection of hereditary metabolic disease in the newborn, an increasingly larger number of patients who may benefit from appropriate nutritional therapy will be identified very early in life. For example, calculations based on the current birth rate and apparent incidence of phenylketonuria indicate that as many as 4,000 infants with this disorder in the United States alone could require dietary therapy in the next decade. There is, therefore, a need to evaluate the principles governing nutritional management of hereditary metabolic disease in order to develop optimal treatment facilities for use in conjunction with new detection methods. It seems anomalous that comparatively little has been done either to establish good treatment practices in hereditary metabolic disease or to mobilize scientific resources to ensure an optimistic outcome for therapeutic endeavors, while so much emphasis has been placed on detection.

Dietary treatment of hereditary metabolic disease is simple in theory; however, practical application may be unexpectedly difficult, or even hazardous, if not carefully supervised. It should be determined whether: (1) the untreated disease is in fact harmful, (2) the treatment is useful in preventing or reversing the unfavorable progression of the disease, (3) the therapy may be harmful by interfering with growth or development, and (4) the program may be harmful to others to whom it is inadvertently or inappropriately given. Management begins with confirmation of the diagnosis by methods more specific than those used in any screening program and continues with monitoring of the biochemical and biological response to dietary manipulations. This memorandum discusses these and other general principles. A handbook of treatment is not intended, and referral to the comprehensive sources identified in Table I is recommended for those requiring detailed information about particular diseases.

GENERAL PRINCIPLES

The events depicted in Figure 1 underlie all types of hereditary metabolic disease. Mutation in the genome, in one way or another, modifies a protein gene product. The gene product is called an apoenzyme when the protein directs a specific biochemical reaction. The association of a low-molecular weight compound or coenzyme (3) may also be required by the apoprotein to achieve optimal catalytic rates; the combined apoenzyme-coenzyme complex is called the holoenzyme. Conversion of one compound [substrate (1)] into another [product (2)], or transfer of unmodified substrate from one side of the membrane to the other, often against an electrochemical gradient, constitute the principal types of "enzymatic" activity.

The inherited disorders of cellular metabolism and transport reflect alterations in structure, activity, or amount of enzyme. Most of the diseases exhibit simple Mendelian inheritance and are the result of mutation at a single genetic locus. Altered biochemical relations and associated clinical consequences constitute the phenotype of such a disease. Specific phenotypes can be described for almost all of these metabolic diseases.

Ideal treatment would restore the normal genetic code as well as subsequent trans-
# NUTRITION IN METABOLIC DISEASE

## TABLE I

**Types of Hereditary Metabolic Disease Apparently Amenable to Therapy**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Therapy Which Has Been Attempted</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorders of Amino Acid Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential Amino Acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylketonuria (classical)</td>
<td>Phenylalanine restriction</td>
<td>61, 62</td>
</tr>
<tr>
<td>Branch-chain ketoaciduria (maple syrup urine disease)</td>
<td>See also Table III</td>
<td>63, 64, 65</td>
</tr>
<tr>
<td>Hypervalinemia</td>
<td>Restriction of leucine, isoleucine, and valine</td>
<td>39, 40</td>
</tr>
<tr>
<td>Isovalericacidemia† (“sweaty-feet” syndrome)</td>
<td>Valine restriction</td>
<td>66</td>
</tr>
<tr>
<td>Homocystinuria, with methioninemia</td>
<td>Protein restriction</td>
<td>67</td>
</tr>
<tr>
<td>Histidinemia</td>
<td>Methionine restriction and cystine supplementation</td>
<td>68, 69, 69a</td>
</tr>
<tr>
<td>Hyperlysinemia</td>
<td>Early histidine restriction (?)</td>
<td>70</td>
</tr>
<tr>
<td>Non-Essential Amino Acids</td>
<td>Protein restriction 1.5 gm/kg/day (see also diseases of urea cycle)</td>
<td>71, 72, 73</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Tyrosine restriction and phenylalanine adjustment</td>
<td>53, 53a</td>
</tr>
<tr>
<td>Diseases of urea cycle</td>
<td>Protein restriction 1-ascorbic acid 75 to 100 mg/day</td>
<td>45, 46</td>
</tr>
<tr>
<td>hyperammonemia</td>
<td>Protein restriction for control of NH₃ intoxication</td>
<td>74</td>
</tr>
<tr>
<td>carbamylphosphate synthetase deficiency</td>
<td>Protein restriction for control of NH₃ intoxication</td>
<td>75</td>
</tr>
<tr>
<td>ornithine transcarbamylase deficiency</td>
<td>Protein restriction for control of NH₃ intoxication</td>
<td>76</td>
</tr>
<tr>
<td>citrullinemia</td>
<td>Arginine supplementation in early infancy (?)</td>
<td>77</td>
</tr>
<tr>
<td>argininosuccinaciduria</td>
<td>Protein restriction</td>
<td>78</td>
</tr>
<tr>
<td>The hyperglycinemias</td>
<td>Protein restriction (about 1 gm/kg/day)</td>
<td>79</td>
</tr>
<tr>
<td>acetonuric form</td>
<td>Protein restriction?</td>
<td>80</td>
</tr>
<tr>
<td>hypo-oxaluric form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders of Amino Acid Transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>Nicotinic acid supplements; good general nutrition</td>
<td>81, 82</td>
</tr>
<tr>
<td>Tryptophanuria‡</td>
<td>Nicotinic acid</td>
<td>83</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>Water; D-penicillamine</td>
<td>84, 85</td>
</tr>
<tr>
<td>with malabsorption or protein intolerance§</td>
<td>Variable</td>
<td>86, 87</td>
</tr>
<tr>
<td>Methionine malabsorption</td>
<td>Protein restriction</td>
<td>88</td>
</tr>
<tr>
<td>Tryptophan malabsorption (blue diaper syndrome)</td>
<td>Protein restriction</td>
<td>89</td>
</tr>
<tr>
<td>Miscellaneous Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₆ dependency syndromes</td>
<td>Pyridoxine HCl (10 mg/day or more)</td>
<td>7</td>
</tr>
<tr>
<td>cystathioninuria</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>vitamin B₆ dependency and seizures</td>
<td></td>
<td>90, 90a</td>
</tr>
<tr>
<td>familial xanthurenic-aciduria</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>familial pyridoxine responsive anemia</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>Folic acid diseases</td>
<td>None known Histidine restriction?</td>
<td>93</td>
</tr>
<tr>
<td>formiminotransferase deficiency</td>
<td>Folic acid</td>
<td>94</td>
</tr>
<tr>
<td>FIGLU’uria, MD magaloblastic anemia and ataxia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Citation is either to a recent article, review, or “classical” paper, whichever provides the most useful information and bibliography concerning treatment.

† L-valine metabolism per se is not abnormal in this disorder affecting the degradation of the equivalent hydroxy acid.

‡ This may be a disorder of tryptophan pyrroline activity, and hence classified under essential amino acids.

§ Whether this constitutes disease separate from the three genotypes of cystinurias or is merely interesting associative phenomena is not clear.
### Disorders of Carbohydrate Metabolism

| Disorder | Therapy Which Has Been Attempted | Reference*
|----------|----------------------------------|--------------
| Hyperglucemia (Childhood Diabetes Mellitus) | Dietary control Insulin | 95 |
| Hypoglycemia  
   - toxic (EDTA, salicylates, sulphonylureas, MOA inhibitors, etc.)  
   - leucine sensitivity  
   - idiopathic  
   - ketotic  
   - deficient catecholamine response  
   - Hyperinsulinism | Remove cause  
   - IV glucose  
   - Protein restriction (steroids)  
   - Steroids  
   - Frequent feeding  
   - Ephedrine  
   - Diazoxide  
   - Surgery | 96, 97, 98, 101, 102, 103, 104, 98, 106 |
| Glycogen storage diseases (Type I-IX) | Galactose restriction (need may be transient) (Pregnancy—special need for Rx of mother) | 41, 107 |
| Galactosemia (4 types: see text) | Restriction of fructose intake | 108, 109 |
| Fructose intolerance | Restriction of dietary carbohydrate | 110, 111 |
| Glucose-galactose malabsorption | Restriction of dietary carbohydrate (excluding glucose) | 112 |
| Fructose-galactose intolerance | | |
| True congenital disaccharidase deficiency | Long-term dietary restriction of offending disaccharide | 113, 114, 115, 116, 117 |
| Acquired disaccharidase deficiency | Temporary restriction of offending disaccharides | 118, 117 |

### Disorders of Lipid Metabolism

| Disorder | Therapy Which Has Been Attempted | Reference*
|----------|----------------------------------|--------------
| Familial hyperlipoproteinemia—3 types:  
   - hyperchylomicronemia  
   - increased β-lipoprotein  
   - increased pre β and β-Lp  
   - increased pre β-Lp  
   - combined hyper β-Lp and hypochylomicronemia | Varies with type—includes:  
   - Medium chain triglyceride supplement  
   - Restriction of cholesterol  
   - Restriction of CHO | 119 |
| Abetalipoproteinaemia | Polyunsaturated FA-supplement | 120 |
| High density lipoprotein deficiency (Tangier disease) | Low fat diet  
   - (None required usually) | 121 |

### Miscellaneous

| Disorder | Therapy Which Has Been Attempted | Reference*
|----------|----------------------------------|--------------
| Gastrointestinal disorders  
   - gluten sensitive enteropathy  
   - cystic fibrosis (intestinal component)  
   - trypsinogen deficiency | Gluten restriction  
   - Pancreatic enzyme replacement  
   - Trypsinogen replacement | 122, 122a, 123, 124 |
| Disorders of mineral metabolism  
   - idiopathic hypercalcemia  
   - vitamin D dependency  
   - renal phosphorus transport | Avoid vitamin D excess  
   - Vitamin D 50,000 units/day  
   - 10 to 20 gm neutral phosphate salt solutions (+ vitamin D in some cases) | 125, 126, 127 |
| Wilson’s disease | D-Penicillamine | 128 |
| Disorders of pyrimidine metabolism  
   - familial hyperuricaemia with finger chewing and MR  
   - oroticaciduria | Probencid, Alkalization  
   - Uridine p.o.  
   - 150 mg every 4 to 6 hours | 129, 130, 5 |

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* This abnormality probably reflects an exaggeration of a normal mechanism reducing hepatic glucose production rather than a genetically controlled metabolic abnormality.99-100

* There is no evidence that the abnormality in adrenalin production in certain patients results from an hereditary enzymatic defect. Rather, it probably results from exhaustion of the chromaffin system.109
scription and translation. This dynamic approach is presently impossible and, therefore, "treatment" must accept as reasonable goals the modification of the biochemical environment in an attempt to offset the mutation, and thereby restore the normal phenotype. Even under these circumstances, one may question whether such treatment modifies only certain biochemical derangements or alters the entire disease process.

Limitation of Substrate

Some abnormal and unfavorable phenotypes may be determined predominantly by accumulation of substrate which is not properly metabolized. Alternatively, the production of metabolites which are themselves toxic and chemically related to or derived from the substrate may establish the phenotype. Dietary restriction of substrate or its precursors should prevent or reduce accumulation and, under these circumstances, ameliorate the harmful phenotype.

Supplementation of Product

If the phenotype is primarily determined by deficiency of product which cannot be synthesized, then appropriate supplementation should restore biochemical relations and the normal phenotype. The inborn errors of hormone biosynthesis are examples in the category. The addition of uridine to the diet in the treatment of orotic aciduria is the most dramatic example in man of true auxotrophism offset by replacement therapy.

Supplementation of Coenzyme

The function of certain apoenzymes may be impaired by mutations compromising absorption or biosynthesis of coenzyme. Dietary supplementation of coenzyme under these circumstances is analogous to "product replacement." Other types of mutation may specifically alter the coenzyme binding site on the apoenzyme. This has been described for pyridoxal phosphate binding by tryptophan synthetase in a mutant strain of Neurospora crassa; it is believed that a similar mechanism may underlie some human inborn errors. Sufficient dietary supplementation with the vitamin precursor is believed to offset the unfavorable binding affinity and has already proven to be simple and effective therapy for this type of hereditary metabolic disease.

Replacement of Gene Product

This is possible when natural or synthetic sources of the normal gene product are available and when it can reach the normal site of action or, conversely, when the substrate can diffuse to it. The management of hemophilia by plasma infusion is a classical example of gene product replacement.

Other Forms of Therapy

It may be impossible to offset the effect of a particular hereditary metabolic disease by any of the foregoing "environmental" approaches, and more peripheral measures may be required (the use of chelation therapy to remove tissue copper in Wilson's disease, or high free-water intake in cystinuria to enhance urinary excretion of cystine). Direct attack on the defect in genetic coding and translation (genetic engineering) should not be ignored, and advances in this direction could render nutritional manipulations obsolete in the treatment of hereditary metabolic disease. Enzyme induction and repression are already being evaluated, and these techniques should provide increasingly important opportunities in the future.

PROBLEMS IN DIETARY MANAGEMENT

General Comments

Therapeutic regimes which involve replacement of product, coenzyme, or apoenzyme are usually simple; general nutritional factors are not compromised and the efficacy of therapy is rapidly apparent. Greater difficulty is encountered in those diseases where arduous restriction of substrate intake is required. When an essential amino acid is involved (Table I and Table II), it is difficult to devise a diet restricted in the content of the amino acid without recourse either to a mixture of pure amino acids or to an isonitrogenous protein.
acids prepared laboriously to specifications or to the use of a specially treated protein hydrolyzate, which is often unacceptable because of unpleasant taste and smell. The preparation of the number and the variety of diets necessary to treat several hereditary metabolic disorders potentially amenable to nutritional management represents a major technical challenge at the present time.

Consumption of a diet limited in an essential nutrient has a distinct hazard, generally more so for younger, more rapidly growing children than for older children or adults, for deficiency of the restricted nutrient can result if intake is too limited (Fig. 2). Therefore, careful clinical evaluation and frequent biochemical monitoring of the appropriate biological fluids must be employed as guidelines to regulate therapy.

In some instances, it may be possible to restrict either pool size or concentration of the offending metabolite, even if the compound is formed endogenously and is not an "essential" nutrient. In some "non-essential amino-acidopathies" (Table II) protein restriction may be sufficient to achieve the desired effect. In other circumstances, however, rigid restriction of protein intake is of no benefit (Table II) and alternate methods of treatment, such as the introduction of an alternate block in the biosynthetic pathway of the compound,* or facilitation of enhanced elimination of the offending compound in the intestine, the urine, sweat, etc. may be required.

Regimes seeking substrate restriction challenge the usual dietary balance; under these circumstances, special attention to nutritional aims and hazards is indicated.

Protein

Dietary protein is the principal source of nitrogen and of essential amino acids.† Non-essential amino acids can be synthesized endogenously if sufficient nitrogen is available and calories are adequate. An abundant dietary intake of non-essential amino acids will reduce the demand on es-

* Therapy of oxalosis has eluded all efforts at treatment until now. Administration of calcium carbimide, however, prevents synthesis of the insoluble oxalic acid by interposing an induced artificial block in the biosynthetic pathway. Preliminary results of this treatment look promising.*
† Valine, leucine, isoleucine, threonine, methionine, phenylalanine, lysine, and tryptophan (possibly histidine in early infancy).††

Fig. 1. A simple scheme depicting the sequence linking the gene to a specific cellular biochemical reaction. A change in genetic information (mutation) may alter the reaction rate. The equilibrium is therefore changed; product deficiency and/or substrate accumulation will occur, either one of which may be important determinants of the total clinical phenotype. Treatment usually includes one of the four basic approaches indicated here; other measures may also be required.

(1) SUBSTRATE RESTRICTION (2) PRODUCT REPLACEMENT (3) COENZYME (VITAMIN) SUPPLEMENT (4) ENZYME REPLACEMENT
NUTRITION IN METABOLIC DISEASE

TABLE II

Examples of Aminoacidopathies in Which Substrate Limitation Has Been Attempted

<table>
<thead>
<tr>
<th>Disease</th>
<th>Nutrient Limited</th>
<th>Biochemical Control With Diet</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>Phenylalanine</td>
<td>Yes</td>
<td>64</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>Leucine, isoleucine, and valine</td>
<td>Yes</td>
<td>39, 40</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Methionine + L-cystine supplement</td>
<td>Yes (partial)</td>
<td>68, 69</td>
</tr>
<tr>
<td>Hereditary tyrosinemia and tyrosyluria</td>
<td>Tyrosine (+phenylalanine adjustment)</td>
<td>Yes</td>
<td>53, 53a</td>
</tr>
<tr>
<td>Hyperglycinemia</td>
<td>Protein</td>
<td>Yes</td>
<td>79, 131</td>
</tr>
<tr>
<td>Hyperlysinemia</td>
<td>Protein</td>
<td>Partial</td>
<td>72</td>
</tr>
<tr>
<td>Urea cycle diseases</td>
<td>Protein</td>
<td>Yes</td>
<td>74</td>
</tr>
<tr>
<td>Isovalericacidemia</td>
<td>Protein</td>
<td>Yes</td>
<td>67</td>
</tr>
<tr>
<td>Hyperprolinemia</td>
<td>Protein</td>
<td>No</td>
<td>131</td>
</tr>
<tr>
<td>Hydroxyprolinemia</td>
<td>Protein and ascorbate</td>
<td>No</td>
<td>132</td>
</tr>
<tr>
<td>Hyper-β-alaninemia</td>
<td>Protein, purines</td>
<td>No</td>
<td>133</td>
</tr>
</tbody>
</table>

essentiaal amino acids for energy purposes and increase the availability of essential amino acids for protein synthesis. In the normal diets, protein should supply 10 to 20% of the calories.

Nitrogen balance reflects intake and loss; the latter includes urinary, fecal elimination, and epidermal replacement. The provision in the diet of an amount of protein sufficient to maintain nitrogen balance will by itself assure sustained normal growth. However, the "biological value" of the protein—a measure of content and availability of essential amino acids—must also be considered. More protein with a low biological value is required to promote a growth rate equivalent to that achieved with a protein of high biological value. Figure 2 depicts an infant who was accidentally rendered phenylalanine deficient while receiving an "adequate intake" of calories and protein; satisfactory growth occurred only when sufficient L-phenylalanine was supplied in the diet.

An appropriate mixture of free L-amino acids (not supplied as protein) given in adequate amount should support adequate growth, and preliminary estimates of the daily requirements in the human infant for amino acid intake in this form have been published. The feeding technique with free amino acids may be of importance. Cannon demonstrated many years ago that amino acids given separately at intervals did not support normal growth rates in rats. Imbalance in the amino acid composition of the synthetic diet can also impair growth. The use of wholly synthetic diets to supply protein needs in infants with certain hereditary metabolic disease (branch-chain-ketonuria below) presents problems, for under these conditions the total nitrogen (amino acid) needs for growing subjects, the percentage of calories that must come from amino acids, and the total caloric needs of subjects consuming these diets have yet to be defined.

**Carbohydrate**

Good nutrition can be sustained on diets varying widely in the content of carbohydrate. Under usual dietary conditions, approximately 50% of the calories consumed come from this source. There is no requirement for any specific carbohydrate because protein and fat from the diet may be converted to carbohydrate to meet the metabolic needs of special tissues (brain). However, one has to consider solute load versus a ketogenic diet if a "high protein
low fat” or a “high fat low protein” diet is utilized.

Specific attention to the type of carbohydrate and carbohydrate content of the diet is important in disorders involving metabolism of monosaccharides and disaccharides (Table I). Data on disaccharide content, in particular of table foods, are unfortunately difficult to obtain because of the variable content associated with different growth conditions of the plants and differences in manufacturing processes.15

**Fats**

Fat, an important component of the diet, provides calories efficiently and ensures dietary palatability and facilitates absorption of the fat soluble nutrients, particularly carotenoids. Approximately 25 gm/day will suffice in the healthy adult. Linoleic acid is an essential fatty acid and probably should comprise 1% of total calories to meet requirements in maintaining growth and dermal integrity.16

The effect of ingestion of a supplement of medium-chain triglycerides upon need for and metabolism of polyunsaturated fatty acids17,18 is an aspect of metabolism of current interest. Intestinal absorption of medium-chain triglycerides is not associated with significant changes in the plasma and tissue levels of total lipids and cholesterol in plasma and tissue decrease. The applicability of these observations to the prolonged treatment of a disease such as familial hyperchylomiconemia is still unknown.

**Vitamins and Minerals**

Attention must be given to the vitamin and mineral intake of children receiving semi-synthetic or wholly synthetic diets.29,31 It is unlikely that a single proprietary diet will meet the individual needs of all patients, and prescription for requirements should be calculated for each patient.

**SPECIFIC ILLUSTRATIONS**

The foregoing general comments can be amplified by specific illustration. Typical problems are described in the following examples. The need for continuing reappraisal of our current knowledge is obvious. There is already ample indication that careful monitoring of the biochemical and clinical progress of the patient with a hereditary metabolic disease is essential if untoward or unpredicted results of management are to be avoided.

**Phenylketonuria**

The most intensively studied of the aminoacidopathies, phenylketonuria, has served as the prototype for the develop-
Condition                        | Typical Plasma Phenylalanine Concentration mg/100 ml | Dietary Phenylalanine Tolerated mg/kg/day* | Reference |
---                                |-----------------------------------------------|------------------------------------------|-----------|
Classical phenylketonuria          | >15                                          | 25 approximately                        | 61, 62, 63, 64 |
Atypical phenylketonuria with high phenylalanine tolerance | >15                                          | 50,† or more                            | 63        |
 transient hyperphenylalaninemia with or without phenylketonuria | >15→N                                        | 25→N                                   | 135       |
Mild persistent hyperphenylalaninemia without phenylketonuria | <15                                          | N                                      | 136†      |
Heterozygote (classical, under certain conditions) | N-8                                          | N                                      | 137       |
Prematurity                        | 4-15                                         | N                                      | 46, 47    |
Technical artefact                 |                                              |                                         |           |

* For mature infant; requirements are higher for all periods during greater growth.
† Few publications yet; verbal communications from many centers, and personal observations by the Committee on Nutrition suggest this condition may not be uncommon. There is no good evidence that the phenotype is heterozygous for the classical condition.
N = Normal amount.

Table III

The Hyperphenylalaninemas
(Tentative Classification)

Management of dietary management in other diseases. However, unanticipated problems have arisen as the therapeutic programs have been applied to the relatively large numbers of affected subjects identified as a result of the screening programs for phenylketonuria. The objectives of screening programs in the newborn period are to detect the affected patient sufficiently early to initiate treatment and to prevent the consequences of the disease when possible. Hyperphenylalaninemia, rather than phenylketonuria itself, has been chosen as the index in most programs now screening for the disease. However, hyperphenylalaninemia is not synonymous with phenylketonuria. There are several other conditions in which hyperphenylalaninemia is also exhibited in the newborn period (Table III). Some of these conditions have been recognized only since mass screening began, and more are probably awaiting recognition. There is no indication at present that dietary treatment of all forms of hyperphenylalaninemia is indicated. Restriction of phenylalanine intake in the empirical manner employed for treatment of “classical” phenylketonuria can cause phenylalanine deficiency in patients with other forms of hyperphenylalaninemia just as it can in “classical” phenylketonuria. Phenylalanine deficiency, whether in patients with phenylketonuria or normal individuals, can cause growth failure, rashes, alopecia, bone changes, marrow abnormalities with anemia, generalized aminoaciduria, and even death. These unfortunate experiences and the confusion arising from failure to distinguish a phenocopy from the primary disease necessitate considerable caution in the management of hyperphenylalaninemia and other, similar aminoacidopathies.

It is obvious that the specific form of the aminoacidopathy must be identified before treatment is begun. Simplified, but perhaps overcategorical, guidelines have been proposed for the use of low phenylalanine diets. The biochemical efficacy of the dietary program must be monitored frequently, and any inappropriate response in levels in the blood of the relevant metabolite or lack of weight gain should alert the physi-
cian to the possibility of an atypical situation. Reliable techniques are available for collection of samples in the home\textsuperscript{30-32} so that the sample may be mailed to a laboratory for analysis. There is, therefore, no technical impediment to frequent monitoring of dietary control.

Even careful attention to levels of phenylalanine in blood cannot yet guarantee success, since a number of patients have failed to respond to dietary manipulations and, more important, not all authorities agree on the range of levels compatible with effective treatment. To add to the confusion, a number of individuals with phenylketonuria (typical genotypes) who experience no dietary manipulation have none of the neurological or intellectual stigmata of the disease.

How long dietary treatment should be continued in the lifetime of the patient is still unknown. Homer and co-workers\textsuperscript{33} and others\textsuperscript{3} have suggested that dietary therapy is probably unnecessary after the fourth year of life. However, while this suggestion may only reflect the greater difficulty there is in maintaining good dietary control in older patients, it may indeed represent a medical fact. Nevertheless, skepticism is indicated concerning a categorical statement about early cessation of diet until more data are available. Human brain growth is not complete by the fourth year of life, and a number of important functions (language) develop at a later age. The metabolic processes presumably impaired in untreated phenylketonuria may be vulnerable at any age, though the evidence for this is speculative; the proposal that phenylketonuric patients who discontinue use of the diet may develop schizophrenia\textsuperscript{52} further restricts the making of any firm recommendation on this issue.

The technique for dietary management and its need during pregnancy for the woman of known homozygous phenylketonuric genotype needs to be assessed. Maternal hyperphenylalaninemia appears to be harmful to the human fetus\textsuperscript{46} and is frequently associated with mental retardation in the offspring regardless of the latter's genotype.\textsuperscript{37} Hyperphenylalaninemia in the pregnant experimental animal\textsuperscript{13} also causes transplacental hyperphenylalaninemia and impaired postnatal performance of the litter. On the other hand, it must be appreciated that induction of phenylalanine deficiency during pregnancy may be equally injurious to the fetus.

**Branch-Chain Ketonuria (Maple Syrup Urine Disease)**

The principles of dietary management illustrated by phenylketonuria may also apply to branch-chain ketonuria. The apparent rarity of the disease and high mortality among the affected, in addition to the difficulties in preparing what is believed to be the appropriate diet, have made the collection of information about treatment difficult. The experiences of Westall\textsuperscript{39} and of Holt and Snyderman\textsuperscript{40} represent the most complete documentation presently available and indicate the potential usefulness of special diets in this disease. Two particular features concerning dietary management merit comment. Growth failure occurred in most patients fed the totally synthetic diet,\textsuperscript{4} even though all nutrients were apparently present in adequate amounts. Growth improved when yeast was added to the diet. The possibility that a relative methionine deficiency caused the growth failure has been considered. The difficulties in defining a "completely adequate" synthetic diet are evident in this situation.

This disease presents a special problem since there is a rapid reappearance of neurological symptoms when patients develop an abrupt rise in plasma concentration of branch-chain amino acids, particularly if initiated by infection.\textsuperscript{13} Early detection of the biochemical deterioration by the use of monitoring techniques would provide a better opportunity to maintain biochemical homeostasis.

**Galactosemia**

This disease is another example of the efficacy of substrate restriction as a mode of
therapy; long-term therapy is indicated for the typical patient. However, it is now apparent that abnormal "galactosemia" is not a homogeneous mutant phenotype or genotype. In addition to the classical disease, there are at least three phenocopies of galactosemia caused by a mild (Durate) variant, a "mosaic" type of transferase deficiency, and by galactokinase deficiency. The precise role of dietary therapy in the latter three diseases is unknown at present. The precautions presented in detail for the management of hyperphenylalaninemia would also apply to patients with galactosemia if they received a wholly or partially synthetic diet. There is no reason to believe that a galactose-free diet per se presents any hazard, since this sugar is synthesized by the human.

Tyrosinemia

Tyrosinemia is the most common aminoacidopathy occurring in man. A transient form of tyrosinemia is common in the newborn, in whom manifestation is dependent upon the intake of protein, as well as of ascorbic acid, and on gestational age of the infant. This form of tyrosinemia may be associated with levels of tyrosine in plasma manyfold above normal and yet is not known to be harmful to the infant. The condition is related to delayed development of the para-hydroxyphenylpyruvic acid oxidizing system which results in tyrosuria (the only manifestation of the disorder) and can be reversed either by temporarily reducing the intake of protein or by increasing the intake of a reducing agent such as L-ascorbic acid.

A second less common form of tyrosinemia associated with tyrosuria is now being recognized throughout the world and may be at least as common as phenylketonuria. The condition is hereditary and is persistent postnatally, and it cannot be ameliorated by ascorbic acid or by modest protein restriction. Only stringent restriction of tyrosine and phenylalanine intake by dietary control beginning early in life can prevent development of hepatic and renal damage and begin to restore a normal biochemical phenotype.

Vitamin Dependencies

There are at least two types of vitamin dependencies; one group involves vitamin B6 and the other vitamin D. These diseases manifest no evidence of deficient intake nor of aberrations in endogenous metabolism of the particular vitamin. However, an augmented daily intake of vitamin is required to maintain a normal phenotype. Occurrence of the diseases is often familial in a pattern indicative of Mendelian inheritance.

The vitamin B6-dependency syndromes are the best studied. There are four recognized syndromes affecting independently cerebral metabolism, blood formation, cystathionine metabolism, and tryptophan metabolism. In each syndrome it has been hypothesized that the abnormal vitamin requirement may be attributed to a genetic modification of coenzyme binding by the pertinent apoenzyme. Evidence in support of this hypothesis has been found in the case of cystathioninuria.

The term, vitamin D dependency, is now being proposed to describe a hereditary form of vitamin D responsive rickets associated with hypocalcemia, hypophosphatemia, and, in most cases, hyperaminoaciduria. The daily requirement of vitamin D is 100 times the normal in this disease. Evidence for vitamin D responsive impairment of calcium transport in the intestine is present. Treatment is simple and, at least with respect to most of the stigmata, effective; but, the dependency appears to be permanent.

Enzyme Replacement

Diseases such as cystic fibrosis of the pancreas, trypsinogen deficiency, and the hemophlias have the advantage that natural sources of the gene product are available and can be delivered to their normal site of action. In diseases such as diabetes mellitus and diabetes insipidus, the appropriate protein hormones are adminis-
tered to maintain homeostasis; replacement of the hormone in these instances is analogous to replacement of enzyme.

Many technical advances will be required before this direct approach to therapy may be applied in other hereditary metabolic diseases. The production of synthetic enzymes will require a knowledge of their primary structure. Experience gained from resolving the structures of hemoglobin, of insulin, of ribonuclease, and of other proteins suggests that the structure of many proteins, including enzymes, may soon be known. When this information is available, it should be possible to consider biochemical synthesis of these proteins, a task which might be facilitated by the new techniques of automated polypeptide synthesis. The effective use of such enzymes will then depend upon achieving contact with substrate. The use of semipermeable microcapsules to contain the enzyme in the vascular compartment is currently under investigation. Finally, transplantation of an organ or of cultured normal human cells must be considered as a possible sustained source of natural enzymes. Prospects for direct attack on the genetic apparatus at one point or another are also of interest, but discussion in this area is beyond the scope of this memorandum.

PRESENT AND FUTURE

The impact of screening programs upon diagnostic and therapeutic resources represents a problem of increasing magnitude. Patients with neonatal biochemical imbalance requiring no treatment must be segregated from infants with the permanent hereditary conditions who do require treatment and identification. Only when phenocopies of the primary diseases are distinguishable will it be possible to identify the specifics of any treatment regime. Moreover, we can perceive the most likely outcome of our efforts at treatment in only a few of the hereditary metabolic diseases; in many others we are either ignorant of what to do or we lack the resources to do what might be done. Treatment centers may have to be organized in order to gather sufficient information quickly and accurately before treatment of most hereditary metabolic diseases can become a feature of medical practice. A cooperative spirit throughout the scientific community is essential to meet this challenge.

One of the legacies of any current success in screening the treatment of people with hereditary metabolic diseases will be a large population of healthy, but mutant, homozygous women. These women will surely want to bear children; therefore, maternal screening and treatment of some of the diseases throughout pregnancy will emerge as a new challenge to guarantee the offspring a normal intra-uterine environment in which to develop.

In the future, technical advances in the medical sciences may radically alter our present approach to the management of patients with hereditary metabolic diseases. One can also predict that increasing interest in eugenic procedures will probably stimulate efforts at segregation and manipulation of mutant genotypes. However, it is likely that environmental modification by dietary and pharmacological means will be the mainstay of treatment for this group of diseases for many years to come.

Charles U. Lowe, Chairman
David Baird Coursin
Felix P. Heald
Malcolm A. Holliday
Donouch O'Brien
George M. Owen
Howard A. Pearson
Charles R. Scriver
L. J. Filer, Jr., Consultant
O. L. Kline, Consultant

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ometric tests all suggest that the hearing defect is within the cochlea and that it is not rapidly progressive. Onset age has not been established. The employment of more than routine hearing tests, testing of other family members, electoretinograms, and historical information about certain features of familial vision are useful in establishing early diagnosis.

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CORRECTION
There is an error in a footnote to Table I in the Committee on Nutrition Report in PEDIATRICS, 40:290, 1967. The footnote should read:

† L-leucine metabolism per se is not abnormal in this disorder affecting the degradation of the equivalent hydroxy acid.
COMMITTEE ON NUTRITION: NUTRITIONAL MANAGEMENT IN HEREDITARY METABOLIC DISEASE
Pediatrics 1967;40;289

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