67

Nutritional Therapies for Neurological and Psychiatric Disorders

G. Franklin Carl

The major neurological and psychiatric disorders are classified into five general categories (Table 67.1) based primarily on the etiology of the disorder. The epilepsies are resistant to etiological classification. Epilepsies may be genetic, developmental, metabolic, or neurodegenerative. Rather than add epilepsy to each of these categories, the epilepsies are treated separately. However, where a specific metabolic cause for the seizures can be identified, or where the seizures are not the major symptom of the disorder, the disorder will be included in the appropriate other category. For example, biotinidase deficiency causes seizures, but the genetic abnormality is easily identified and treatable with high dose biotin, so for the purposes of this section it will be treated separately under Inborn Errors of Metabolism.

Epilepsies

Epilepsy is a neurological disorder characterized by paroxysmal depolarization of cortical neurons causing the external phenomenon known as a seizure. Epilepsy has many causes, but most seizures stem from a cortical focus in which the depolarization of neurons is uncontrolled. The depolarization may remain confined to a specific area of the cortex or it may generalize from the focus to involve much of the brain. Some forms of epilepsy are nonfocal, initiating with a generalized seizure. The preferred treatment for recurrent seizures is pharmacological.

Antiepileptic drugs are the primary therapy for idiopathic seizures. Phenobarbital, phenytoin, primidone, and ethosuximide were the first line of drugs used to treat seizures in the post-bromide years. They were joined by valproate and carbamazepine in the 1970s. Recently a number of new drugs have been added to the neurologist's pharmacopeia for the treatment of seizures. The newer drugs are being developed to improve efficacy and safety. Side effects include interactions of phenytoin, phenobarbital, and primidone with nutrients including folic acid, carnitine, vitamin D, and vitamin K[1-4] (Table 67.2). Carbamazepine causes increased plasma homocysteine,[5] and valproate has been linked to birth defects.[6] Interestingly, valproate inhibits the folate-dependent glycine cleavage system.[7] It has also been shown to cause carnitine depletion[8] (Table 67.2).

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TABLE 67.1

Classification of the Major Neurological and Psychiatric Disorders and the Potential Response of Each to Nutritional Therapy

Category Disease or Disease Group Specific Diseases	Defining Characteristics of the Disease	Response to Nutritional Therapy	Therapy	References
Epilepsies	A diverse group of idiopathic disorders characterized by spontaneous seizures resulting from recurrent paroxysmal cerebral neuronal firing	++++	Ketogenic diet	10,12-14
Neurodegenerative Diseases				
Parkinson's disease	Degeneration of the nigrostriatal tract leading to tremor, muscular rigidity, bradykinesia, and unstable posture	+++ +++++	MAOI + MAOI diet L-DOPA + low protein diet	16,18 19-21
Alzheimer's disease	Progressive loss of cognitive function associated with the appearance of amyloid plaques and neurofibrillary tangles in the brain	+++ +++	MAOI + MAOI diet Adequate protein and energy intake + supplements with vitamins E, B_1 & B_{12}	18,24 25
Multiple sclerosis	Chronic central demyelinating disease of uncertain cause; may have infectious, autoimmune and genetic components	+ ++	Vitamin D Essential fatty acids	27 28
Amyotrophic lateral sclerosis	Chronic degeneration of motor neuron function; linked to genetic abnormality of Cu/Zn superoxide dismutase	?	? Vitamin E	30
Guam/ALS/Parkinsons/Dementia	Food-induced, chronic degeneration of cells in PNS and CNS	0		32,33
Tardive dyskinesia	Chronic parkinsonian-like syndrome caused by neuroleptics	+++ ?	Choline supplementation ?Vitamin E	35 34
Neurodevelopmental Diseases				
Neural tube defects	Abnormal development of the neural tube in utero	prevention	Folate supplementation periconceptionally	36
Schizophrenia	Psychoses associated with structural abnormalities in the brain	++	Increased requirements for vitamin C essential fats	42 43

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Affective disorders				
Bipolar disorder	Alternating states of mania and depression	++	Choline supplementation	35
		++	n-3 Polyunsaturated fatty acids	48
		+++	Low salt diet	44
Endogenous depression	Depression of mood	++++	S-adenosylmethionine	45,46
		+++	Folic acid	47
		++	n-3 Polyunsaturated fatty acids	48
Hyperactivity	Attention deficit with hyperactivity Disrupts learning	?	Nutritional treatments controversial	
Metabolic Diseases				
Encephalopathies	Metabolic disturbances that affect CNS			
Wernicke-Korsakoff	Thiamine deficiency often induced by alcohol	++++	Thiamine early in disease process	52
Hepatic encephalopathy	Failure of liver to remove neurotoxins from blood	++++	Lactulose and lactitol	51,54
Neuropathies	Metabolic disturbances that affect PNS			
Pyridoxine toxicity	Sensory polyneuropathy	0	Cease vitamin B_6 megadoses	55
Diabetic neuropathy	Slowly progressing, sensorimotor, autonomic polyneuropathy	prevention	Control of blood glucose	57
Vitamin B_{12} deficiency	Dysmyelination leading to parasthesias and weakness	prevention	Vitamin B_{12} early before dysmyelination	56
Pantothenic acid deficiency	Demyelination leading to parasthesias	prevention	Pantothenic acid early before demyelination	56
Inborn Errors (Genetic Diseases)				
Peroxisomal diseases				
Adrenoleukodystrophy	Progressive central demyelination with retardation and death	+++	Lorenzo's oil + polyunsaturated fatty acids	63 64
Refsum's disease	Dysmyelination leading to a polyneuropathy	+++	Lorenzo's oil + polyunsaturated fatty acids	57 64
Maple syrup urine diseases	Defects of branched chain amino acid catabolism leading to accumulation of organic acids causing lethargy, seizures, retardation, coma	++++ ++++	Defined amino acid diet Thiamine, biotin, B_{12} in some patients	66 67
Functional biotin deficiency	Increased plasma organic acids, psychomotor retardation, seizures, ataxia	+++++	High dose biotin, early	66

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TABLE 67.1 *(Continued)*

Classification of the Major Neurological and Psychiatric Disorders and the Potential Response of Each to Nutritional Therapy

Category Disease or Disease Group Specific Diseases	Defining Characteristics of the Disease	Response to Nutritional Therapy	Therapy	References
Glucose Transporter Deficiency	Infantile seizures and developmental delay Low CSF glucose and low to normal CSF lactate	++++	Ketogenic diet	67
Diseases of glycogen recall and gluconeogenesis	CNS symptoms of hypoglycemia between meals with rapid onset	+++++	Frequent small meals	68
Deficiencies of fatty acid beta-oxidation	CNS symptoms of hypoglycemia with starvation or fasting	+++++	Avoid depletion of glycogen stores	68
Pyruvate dehydrogenase deficiency	Lactic acidosis	++	Ketogenic diet	68
			Thiamine, lipoic acid with partially active enzyme	68
Defects in respiratory chain proteins	Muscle weakness, ataxia, pyramidal symptoms	++	Vitamins C and K sometimes partially successful	68
Phenylketonuria	Standard genetic screen Failure to treat causes retardation	+++++	Restricted phenylalanine intake	66,69,70
Homocystinuria	High urinary and plasma homocysteine	++++	Betaine, po	66
	Retardation, psychiatric disorders, vascular damage	+++++	Vitamin B_6, po	
		+++	Vitamin B_{12}, im	
Urea cycle defects	Hyperammonemia causes lethargy and coma in neonates accompanied by high blood glutamine and alanine	++++	Sodium benzoate, po	66
		++++	Phenyl acetate, po	
		+++	Arginine, Citrulline	
Glutamate decarboxylase deficiency	Seizures, prenatal, and neonatal	+++	Pyridoxine, iv	66
Wilson's disease	Copper toxicity causes myriad symptoms including tremor, dysarthria, dysphagia, psychiatric disorders	+++++	Penicillamine	72
		+++++	Trientine	
		++++	Zinc, not with chelators	

Treatment ratings:
- 0 = No known treatment
- + = Suggested or hypothetical treatment
- ++ = Anecdotal evidence for positive effect
- +++ = Treatment shown to have positive effect
- ++++ = Preferred treatment in some cases
- +++++ = Primary treatment

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TABLE 67.2

Known Interactions between Antiepileptic Drugs and Nutrients

Drug	Nutrient	Interaction	Treatment	References
Phenytoin	Folic acid	Can cause folate deficiency; high dose folate treatment can decrease plasma phenytoin	Patients receiving phenytoin should be given folate supplement (1-5 mg/d)	1
	Vitamin D	Appears to induce enzymes that cause increased catabolism of vitamin D	Patients need 500-1200 IU/d of vitamin D	2
	Vitamin K	Appears to induce enzymes that cause increased catabolism of vitamin K	Risk in newborn of epileptic mother taking phenytoin Prophylactic treatment of mother with vitamin K	3 4
Phenobarbital	Folic acid	Causes decrease in plasma folate concentration	see Phenytoin	1
	Vitamin D	Appears to induce enzymes that cause increased catabolism of vitamin D	see Phenytoin	2
	Vitamin K	Appears to induce enzymes that cause increased catabolism of vitamin K	see Phenytoin	3 4
Primidone	Folic acid	Converted to phenobarbital by the liver; has same effect on folic acid as phenobarbital	see Phenytoin	1
	Vitamn D	Converted to phenobarbital by the liver; has same effect on vitamin D as phenobarbital	see Phenytoin	2
	Vitamin K	Converted to phenobarbital by the liver; has same effect on vitamin K as phenobarbital	see Phenytoin	3 4
Carbamazepine	Folic acid?	Causes increase in plasma homocysteine	?	5
Valproate	Folic acid	Linked to birth defects probably via inhibition of the glycine cleavage system	Suggest betaine or choline (5-10 g/d, po) (personal recommendation)	6,7
	Carnitine	Causes plasma carnitine deficiency by a mechanism not yet understood	Oral carnitine prevents hyperammonemia caused by valproate in patients at risk for carnitine deficiency	8

For seizures unresponsive to drug therapy surgery is often the only option, but some patients are not viable candidates for surgery, and for others surgery doesn't work. The ketogenic diet has proven effective in a portion of the intractable epilepsies.[9,10] The ketogenic diet was first proposed by Wilder[11] in response to his observation that fasting often decreased seizure frequency. Before the advent of effective pharmacotherapy, it was the method of choice for the treatment of epilepsy.[10] High fat with low carbohydrate and low protein intake are used to generate ketone bodies as the main energy source to the brain, reducing the concentration of circulating carbohydrate. In addition, the diet lowers the pH of the blood. Some believe that the lowered pH is responsible for the antiseizure effectiveness of the diet. The ketogenic diet has recently been reviewed from a neurologist's perspective[12] and placed in the context of other treatments for epilepsy.[13]

Ketogenic diets are difficult to maintain because of the blandness and monotony of the high fat foods, but support groups are available through a Stanford University web site (http://www.stanford.edu/group/ketodiet), and a set of palatable diets and acceptable substitutes has been generated by Carroll and Koenigsberger[14] (Tables 67.3 through 67.8).

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TABLE 67.3

Sample Menus for the Ketogenic Diet on a 3-Day Rotating Meal Plan (Exchanges for menu items can be picked from Tables 67.4-67.8. Quantities listed are for children ages 1-3. Portions can be increased for older children and adults.)

	Day 1	Day 2	Day 3	Appropriate Exchanges in	Foods and Seasonings That Can Be Used Freely	
Breakfast	1/4 cup corn flakes + 4 2/3 Tbsp heavy cream	1/4 cup cooked oatmeal + 4 2/3 Tbsp heavy cream	1/2 slice wheat bread + 2 1/4 Tbsp margarine	Table 7, starches	Boullion (dilute 1/2 strength) Sugar-free drinks Celery	Basil Cocoa Chives
	2 oz whole milk + 3 1/2 Tbsp heavy cream	2 oz whole milk + 3 1/2 Tbsp heavy cream	1 oz American cheese + 3 Tbsp heavy cream	Table 8, dairy products	Cucumber Iceberg lettuce Endive Pickles (dill)	Cinnamon Curry Dill Garlic powder
Lunch	1 oz cooked chicken + 2 2/3 Tbsp mayonnaise (chicken salad)	1 hardboiled egg + 2 Tbsp mayonnaise (egg salad)	1 Tbsp natural peanut butter + 1 2/3 Tbsp margarine (double butter delight)	Table 5, meats/meat substitutes	Sugar-free gelatin Mustard Vinegar Saccharine, aspartame	Garlic (fresh) Lemon Lemon pepper Lime
	lettuce leaf + 1/4 avocado, sliced + 1 1/2 tsp oil/vingar	1/4 cup cooked carrots, cold + 2 1/2 tsp oil/ vinegar	2 oz tomato juice + 2 Tbsp heavy cream	Table 4, vegetables	Limited extracts of vanilla almond walnut	Onion powder Oregano Paprika Pepper
	1/4 cup pears (water packed) + 3 1/4 Tbsp heavy cream	1/4 cup grapes + 2 2/3 Tbsp heavy cream	1/4 banana + 2 1/2 Tbsp heavy cream (add ice, vanilla, water to make shake)	Table 6, fruits	lemon	Salt
			4 celery sticks	Free use vegetable	Conversions 1 Tbsp margarine = 11.0 g fat	
Dinner	1/2 beef frank + 1/2 tsp margarine	1 oz cooked hamburger + 1 1/3 Tbsp margarine	1 oz fried bologna + 1/2 Tbsp margarine	Table 5, meat/meat substitutes	1 Tbsp oil = 15 g fat 1 Tbsp heavy cream = 5.6 g fat 1 Tbsp mayonnaise = 11.2 g fat	
	1/4 cup cooked carrots + 1 Tbsp margarine	1/4 cup broccoli + 1 Tbsp margarine	1/2 cup chopped asparagus + 1 1/2 Tbsp margarine (cooked)	Table 4, vegetables	1 Tbsp margarine = 3/4 Tbsp oil = 2 Tbsp heavy cream = 1 Tbsp mayonnaise 1 g protein = 4 kcal	
	1 dill pickle			Free use vegetable	1 g carbohydrate = 4 kcal 1 g fat = 9 kcal	

Reference: Carroll J, Koenigsberger D. The ketogenic diet: a practical guide for caregivers.

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TABLE 67.4

Ketogenic Food Exchange for Vegetables[a]

Vegetable	Amount	Fat (Tbsp), Choose One		
		Margarine	Oil	Heavy Cream
Carrots (cooked)	1/4 cup	1	5/6	2
Cauliflower (cooked)	1/2 cup	1 1/4	11/12	2 1/2
Spinach (cooked)	1/4 cup	1	5/6	2
Broccoli (cooked)	1/4 cup	1	5/6	2
Asparagus (cooked)	1/2 cup	1 1/2	1 1/6	2
Green beans (cooked)	1/4 cup	1	5/6	2
Eggplant (raw, chopped)	1/2 cup	1 1/6	1	2 1/2
Sliced beets (cooked)	1/2 cup	1	5/6	2
Collard greens (cooked)	1/4 cup	1 1/4	11/12	2 1/2
Sauerkraut (cooked)	1/4 cup	1 1/4	5/6	2 1/2
Mushrooms (fresh, small)	5 ea	1 1/4	11/12	2 1/2
Avocado (fresh, small)	1/4	3/4	1/2	1 1/4
Pepper (raw, chopped)	1/2 cup	1 1/6	1	2 1/2
Onions (fresh, chopped)	1/4 cup	1 1/4	11/12	2 1/2
Infant carrots (pureed)	1 1/2 oz	1 1/2	1 1/6	2 1/2
Infant green beans (pureed)	1 1/2 oz	1 1/2	1 1/6	2 1/2
Infant spinach (pureed)	1 1/2 oz	1 1/2	1 1/6	2 1/2
Infant squash (pureed)	1 1/2 oz	1 1/2	1 1/6	2 1/2
Infant sweet potato (pureed)	1 oz	2	1 7/12	3 1/2
Tomato juice	2 oz	1	5/6	2

[a] Each row yields 143 kcal with 0.9 g protein, 2.7 g carbohydrate, 14.5 g fat.

Reference: Carroll J, Koenigsberger D. The ketogenic diet: a practical guide for caregivers. Copyright by The American Dietetic Association. Modified with permission from *JADA* 98: 316-321; 1998.

The caloric intake in these diets is designed for young children (one to three years), but the portions can be increased to meet energy needs as the child grows. The diets can be used for adults, with appropriate adjustment of portions. Initiation of the ketogenic diet requires 12 to 38 hours of fasting to generate ketosis to begin the diet. Once in ketosis, the high fat ketogenic diet will maintain ketosis. Patients should be started on the diet gradually, consuming about half of a high fat meal for the first two meals before ingesting whole meals. Carroll and Koenigsberger[14] have found that small amounts of starch will be tolerated by most children, but some are sensitive to starch. Fluids should not be limited, but should not contain sugar.

Neurodegenerative Diseases

Parkinson's Disease (PD)

PD is caused by the usually slow, irreversible degeneration of the dopaminergic nigrostriatal neurons. This destruction may result from any number of pathological circumstances but is often accelerated by the generation of free radicals. Unfortunately, by the time symptoms appear, most of the dopaminergic function in the nigrostriatal pathway has deteriorated. L-3,4-dihydroxyphenylalanine (L-DOPA), the precursor for dopamine, is the primary treatment for PD, but L-DOPA itself has significant toxicity, and its use should be postponed as long as possible.[15] More efficient use of the endogenous dopamine

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TABLE 67.5

Ketogenic Food Exchange for Meats/Meat Substitutes[a]

Meat/Meat Substitute	Amount	Fat (Tbsp), Choose One		
		Margarine	Oil	Heavy Cream
Beef frank	1/2 frank	1/2	5/12	1
Bologna	1 oz	1/2	5/12	1
Cooked steak	1 oz	1 2/3	1 5/12	3 1/2
Cooked hamburger (chuck)	1 oz	1 2/3	1 5/12	3 1/2
Chicken (dark meat, cooked)	1 oz	2 2/3	2	5 1/4
Veal cutlet (cooked)	1 oz	2 1/4	1 2/3	4 1/2
Bacon (use all fat)	3 slices	—	—	—
Ham	1 oz	2	1 1/2	3 2/3
Tuna (in oil)	3/4 oz	1 2/3	1 5/12	3 1/2
Flounder (other fin fish, cooked)	3/4 oz	2	1 1/3	3 1/2
Salami	1/2 oz	1	3/4	2
Pork sausage (cooked)	1/2 link	2	1 1/2	3 2/3
Shrimp (cooked)	3/4 oz	2	1 1/3	3 1/2
Infant beef (strained)	2 oz	1 1/4	1	2 1/2
Infant chicken (strained)	2 oz	1 1/4	1	2 1/2
Infant veal (strained)	2 oz	1 1/4	1	2 1/2
Infant turkey (strained)	2 oz	1 1/4	1	2 1/2
Egg (large)	1	2	1 1/2	3 2/3
Peanut butter (natural)	1 tbsp	1 2/3	1 1/3	3 1/2
Macadamia nut (dry/oil roasted)	1 oz	1/2	1/12	1/4

[a] Each row yields 245 kcal with 6.0 g protein, 24.3 g fat.

Reference: Carroll J, Koenigsberger D. The ketogenic diet: a practical guide for caregivers.

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TABLE 67.6

Ketogenic Food Exchange for Fruits[a]

Fruit	Amount	Fat (Tbsp), Choose one		
		Margarine	Oil	Heavy Cream
Applesauce (unsweetened)	1/4 cup	2 1/2	1 5/6	4 2/3
Apricot halves (water packed)	2 halves	1	3/4	2
Fresh blueberries	1/8 cup	1 1/4	1	2 1/2
Fresh cherries	3	1	3/4	2
Banana (small, 6 inches)	1/4	1 7/12	1 1/4	3
Fresh strawberries	1/4 cup	1	3/4	2
Fresh cantaloupe	1/8 cup	1 1/2	1 1/6	2 2/3
Peaches (water packed)	1/4 cup	1 1/2	1 1/6	2 2/3
Fresh grapes	1/4 cup	1 1/2	1 1/6	2 2/3
Pears (water packed)	1/4 cup	1 2/3	1 1/4	3 1/4
Pineapple (water packed)	1/4 cup	1 2/3	1 1/4	3 1/4
Fresh raspberries	1/4 cup	1 1/2	1 1/6	2 2/3
Fresh, small plum	1/2 plum	1 1/2	1 1/6	2 2/3
Infant apple (pureed)	1 oz	1 1/4	1	2 1/4
Infant apple/pineapple (pureed)	1 oz	1 1/4	1	2 1/4
Infant apricots (pureed)	1 oz	1 1/4	1	2 1/4
Infant peaches (pureed)	1 oz	2	1 7/12	4 1/4
Infant pears (pureed)	1 oz	2	1 7/12	4 1/4

[a] Each row yields 168 kcal with 4.2 g carbohydrate, 17 g fat. If fruit packed in fruit juices, soak in water for 1 hour.

Reference: Carroll J, Koenigsberger D. The ketogenic diet: a practical guide for caregivers.

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TABLE 67.7

Ketogenic Food Exchange for Starches[a]

Food	Amount	Fat (Tbsp), Choose One		
		Margarine	Oil	Heavy Cream
Cereals				
Corn flakes	1/4 cup	2 1/2	1 2/3	4 2/3
Infant dry cereal (oat, barley or rice)	2 tbsp	1 1/2	1 1/6	3 1/4
Cold rice cereal	1/4 cup	2 1/2	1 5/6	4 2/3
Toasted oat cereal	1/4 cup	1 3/4	1 1/4	3 1/4
Cooked oatmeal (regular)[b]	1/4 cup	3	2	5 1/6
Cooked wheat cereal[b]	1/8 cup	1 1/2	1 1/6	3 1/4
Cooked grits[b]	1 oz	1 1/2	1 1/6	3 1/4
Cooked farina[b]	1/4 cup	2 1/2	1 5/6	4 2/3
Bread/Crackers				
Medium bagel (half)	1/4	1 3/4	1 1/3	3 1/3
Bread stick (0.28 oz)	1 1/2	1 3/4	1 1/3	3 1/3
English muffin	1/4	2 3/4	2	5 1/3
Wheat bread (sliced)	1/2	2 1/2	1 5/6	4 3/4
White bread (sliced)	1/2	2 1/2	1 5/6	4 3/4
Frozen waffle	1/3	2 1/4	11/12	4 1/4
Crackers/arrowroot cookies	1	1 3/4	1 1/3	3 1/3
Rice cakes	1/2	1 1/2	1 1/12	2 3/4
Ritz crackers[c]	2	1 7/12	1 1/6	3 1/4
Saltines	2	1 3/4	1 1/3	3 1/3
Triscuits[c]	2	2 1/4	1 7/12	4 1/4
Wheat Thins[c]	4	1 3/4	1 1/3	3 1/3
Zwieback	1	2 1/4	1 7/12	4 1/4
Starchy Vegetables				
Yellow cooked corn (frozen)	1/8 cup	1 3/4	1 1/3	3 1/3
Peas (frozen in butter sauce)	1/8 cup	1 1/2	1 1/12	2 5/6
Cooked potato (mashed)	1/8 cup	1 3/4	1 1/3	3 1/3
Cooked macaroni	1/8 cup	2 1/4	1 7/12	4 1/4

[a] Each row yields 226 kcal with 4.9 g carbohydrate, 0.75 g protein, 22.6 g fat.
[b] Cereal should be cooked in water only.
[c] Trademark of Nabisco, East Hanover, NJ.

Reference: Carroll J, Koenigsberger D. The ketogenic diet: a practical guide for caregivers. Copyright by The American Dietetic Association. Modified with permission from *JADA* 98: 316-321; 1998.

can accomplish this by inhibiting the dopamine catabolizing enzymes, particularly monoamine oxidase, or by protecting the dopamine with antioxidants. Monoamine oxidase itself generates free radicals as a consequence of its catalytic mechanism in the oxidation of dopamine. Of the two monoamine oxidases in the brain, MAO B is the primary catabolizing enzyme for dopamine. Shoulson and the Parkinson Study Group[16] have shown that L-DOPA use can be postponed by the specific MAO B inhibitor, deprenyl (5 mg, bid). However, alpha-tocopherol treatment did not extend the time between diagnosis and the introduction of L-DOPA treatment for Parkinsonian symptoms in the same study. In an uncontrolled study, a combination of alpha-tocopherol (3200 units/d) and vitamin C (3 g/d) was reported to postpone the need to administer L-DOPA.[17] These levels are so high that the investigator gradually increased the daily dose to reach the levels indicated, but found no significant toxicity.

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TABLE 67.8

Ketogenic Food Exchange for Dairy Products[a]

Dairy Product	Amount	Fat (Tbsp), Choose One		
		Margarine	Oil	Heavy Cream
Cheese Products (Measure by Weight)				
Cheddar	3/4 oz	1 1/2	1 1/6	2 1/2
Swiss	3/4 oz	2	1 7/12	3 2/3
Cream cheese	2 tbsp	1/6	1/12	1
American	1 oz	1 1/2	1 1/6	3
Feta	1 oz	1 1/4	1	2 1/2
Mozzarella (whole milk)	1 oz	1 1/2	1 1/6	3
Brie	1 oz	1 1/2	1 1/6	3
Cottage cheese	1 Tbsp	1 1/2	1 1/6	3
Parmesan	1 Tbsp	1/2	1/2	1 1/2
American cheese spread	1 Tbsp	2	1 7/12	4
Milk Products				
Milk (whole)	2 oz	1 2/3	1 1/4	3 1/2
Sour cream	2 Tbsp	1/2	1/6	3
Yogurt (plain)	1/4 cup	2 1/2	1 5/6	5

[a] Each row yields 216 kcal with 0.5 g carbohydrate, 4.7 g protein, 21.7 g fat.

Reference: Carroll J, Koenigsberger D. The ketogenic diet: a practical guide for caregivers. Copyright by The American Dietetic Association. Modified with permission from *JADA* 98: 316-321; 1998.

During the treatment of PD patients with a MAO inhibitor, it is essential that their diet be limited in the content of tyramine. Gardner et al.[18] have analyzed many foods for tyramine content and have proposed a "user-friendly MAOI diet" that is not as restrictive as many other MAOI diets. It appears that any foods that have been processed with microorganisms, whether purposefully or by neglect, are likely to contain high concentrations of tyramine. Such foods include matured or aged cheeses, fermented or dry sausages, foods that have not been properly stored, beverages made by fermentation, certain yeast extracts (Marmite), and sauerkraut. All cheeses except cottage cheese, cream cheese, ricotta cheese, and processed cheese slices should be considered aged or matured cheeses. Pizzas, lasagnas, and many casseroles are made with aged cheeses and should not be eaten when taking MAO inhibitors. Other fresh milk products that have not been allowed to grow fermenting organisms should not contain high levels of tyramine. Fermented or dry meats that have high tyramine levels include pepperoni, salami, mortadella, and summer sausage, among others. Food storage is important in the production of tyramine. Since purposely fermenting foods produces tyramine, neglectful fermenting (poor storage) can also produce tyramine. Foods that have had an opportunity to grow organisms, whether left out at room temperature or stored too long in the refrigerator, should not be consumed by patients taking MAO inhibitors. Meats (all meats) are more likely to produce the tyramine when improperly stored because of the higher protein content of meats. Cooking will destroy the organisms but not the tyramine, so do not assume that cooking will make the meat fit for consumption for the patient. Beer and wine are produced by fermentation processes. Tap beers have high tyramine levels and should be totally avoided, but bottled (canned) beers and wines can be consumed in moderation (no more than two drinks/day; 16 oz. of beer/d, 8 oz. of wine/d). Other foods to avoid are fava, broad bean pods (not the beans), banana peels (not the banana pulp), and soy condiments (not soy milk). Other

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TABLE 67.9

Protein Content in Common Foods

Food	Protein Content
Eggs	3.5 g/oz
Milk	8.0 g/cup
Cheeses	7.0 g/oz
Meats, lean beef, poultry, pork, fish	6.9 g/oz
Fruits (apples, figs, plums, and grapes are low in protein)	0.5-1.4 g/cup
Fruit juices	1.0-1.4 g/cup
Breads	2.0 g/slice
Cereal	2.0-4.0 g/cup
Pasta	4.0 g/cup
Rice, cooked	4.0 g/cup
Fats, butter, oils, mayonnaise	trace
Vegetables	2.0-3.4 g/cup
celery	4.0 g/cup
Low protein calorie supplements	
porridge, low protein	0.13 g/cup
noodles, low protein anellini, ragatoni, tagliatelle	0.2 g/cup
bread, low protein	0.1 g/slice
cranberry sauce	0.4 g/cup
honey	0.07 g/tsp
jelly	0.05 g/Tbsp
jam	0.03 g/Tbsp
mints	trace
jelly beans	0.1 g/oz
hard candy	0.1 g/oz
table syrup	0.05 g/Tbsp
marshmallows	0.03 g ea
cranberry juice	0.01 g/oz
Hi-C	0.01 g/oz
Sodas	0.01 g/oz
Dessert topping	0.3-0.6 g/cup

Reference: Burtis G, Davis J, Martin S. *Applied Nutrition and Diet Therapy* W.B. Saunders, Philadelphia, 1988, pp. 784-787.

than those items identified here as tyramine containing or potentially tyramine containing, most foods are allowed on the "user-friendly MAOI diet."

Once treatment with L-DOPA starts, it is necessary to rearrange the protein in the diet of PD patients to maximize the effect of the L-DOPA.[19-21] Because many of the amino acids (the large neutral group) will compete with L-DOPA for uptake into the brain, it is best to ingest the protein when the amino acid competition will have the least detrimental effect. Protein is essential, but if good quality protein is ingested (eggs, milk) the requirement can be reduced to 45 g/d for the average size adult. If the majority of the dietary protein (>80%) is consumed in the evening, the effects of the competition between the amino acids and L-DOPA will be minimized because the decreased L-DOPA uptake into the brain will occur during the night when the patient is asleep and when, presumably, the increase in involuntary movements will be least disruptive. Protein contents of common foods are shown in Table 67.9.

Because constipation is a problem in PD patients, it is recommended that adequate amounts of fiber and fluid be ingested.[22] Ingestion of low protein grains, vegetables, and fruits during the day with at least 64 oz. of water or other non-protein containing drink should accomplish this goal.

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Alzheimer's Disease

Alzheimer's disease is characterized by progressive cognitive loss. Early effects appear to involve cholinergic projections from the basal forebrain. Later disease seems to affect many different cell populations, involving several of the neurotransmitters. A diagnosis of Alzheimer's disease is confirmed postmortem by the identification of the typical neurofibrillary tangles and senile plaques. Free radical damage is suspected as a mechanism of cell loss in Alzheimer's, but confirmation is elusive. However, work with Down's syndrome patients and results from the Nun study[23] indicate that mechanisms leading to Alzheimer's may be operative well before cognitive symptoms appear. There is no cure for Alzheimer's or even a moderately effective treatment. It is possible, however, to ameliorate the symptoms and prolong life in these patients with appropriate treatment and diet. As with PD patients, inhibition of the MAO-B (5 mg deprenyl, bid) appears to be effective in conserving transmitter function and prolonging cognitive function.[24] Therefore, Alzheimer's patients treated with MAO-B inhibitors should not eat the tyramine-rich foods discussed in the section on Parkinson's disease. However, unlike PD patients, alpha-tocopherol (1000 IU, bid) is effective in slowing the progress of the Alzheimer's disease,[24] indicating that free radical damage may be a continuing problem in the progression of the disease.

Whether from a chronically poor diet or from an increased need for nutrients, Alzheimer's patients often suffer from protein malnutrition and other nutritional deficiencies that improve the status of the patient when corrected.[25] Whether any of the vitamins has a specific relationship to Alzheimer's is unknown, but vitamin E, thiamine, and vitamin B_{12} have been associated with improvement of symptoms when blood levels are corrected to normal.[25] Vitamin E may help by slowing the rate of free radical-induced tissue damage. Thiamine may help to produce acetylcholine through its participation in the reaction catalyzed by pyruvate dehydrogenase, the rate-limiting step in the synthesis of acetylCoA, a precursor to acetylcholine, the neurotransmitter most closely associated with Alzheimer's symptoms. Vitamin B_{12} is required for the generation of methyl groups that are involved in either the synthesis or the conservation of choline, the other component of acetylcholine. High dose acetyl-L-carnitine (1000 mg with breakfast, 1000 mg with lunch) has also been reported to slow the progression of Alzheimer's disease.[26] Adequate nutriture is essential to preserve as much function as possible.

Multiple Sclerosis (MS)

MS appears to be an autoimmune disease that involves demyelination in the central nervous system. The symptomatology generally progresses slowly and intermittently, but the disease can be fatal. Interestingly, a consistent observation with respect to the etiology of MS is that MS occurs more frequently at higher latitudes. Risk for MS is apparently acquired early in life because one carries the risk associated with the place in which one spends his/her first 15 years. Several hypotheses have been proposed to relate the risk to the disease.

Hayes et al.[27] have hypothesized that the relationship to latitude is a function of the amount of sunlight to which one is exposed. The sunlight activates vitamin D, forming vitamin D_3 which is involved in the regulation of the immune system. Inadequate exposure to sunlight at higher latitudes would create a deficiency in activated vitamin D that translates into an increased risk for development of autoimmune disorders. It has been shown that vitamin D_3 can prevent experimental autoimmune encephalomyelitis (EAE) in mice. EAE is an animal model for MS. Hayes and Ebers are currently examining this hypothesis in a large population at risk for MS (personal communication).

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Several studies (see Bates et al.[28] for review) have indicated that treatment of MS patients with essential fatty acids early in the disease ameliorates the symptoms and slows the progression of the disease. However, these studies make no attempt to explain the geographical differences in the incidence of MS, and the oils used to administer the essential fatty acids to the patients will very likely contain significant quantities of the fat-soluble vitamin D.

To affect the disease process with either essential fatty acids or vitamin D, it is necessary to intervene early in the disease process.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease affecting the motor neurons in the spinal cord, brainstem, and motor cortex. It is linked to genetic abnormalities of Cu/Zn superoxide dismutase (SOD1). Lipid peroxidation has been shown to be higher in ALS patients than in controls.[29] Transgenic mice expressing the mutant human SOD1 exhibit the symptoms of ALS.[30] Dietary supplementation of these mice with vitamin E delayed the onset of symptoms and slowed the progress of the disease but did not prolong survival time. Putative inhibitors of the glutamatergic system increased survival time, indicating that excitotoxicity is a factor in the progression of the disease. However, the glutamatergic inhibitors did not delay the onset of the disease, indicating that different mechanisms are involved in disease induction and disease progression. Nutritionally it would seem advisable to maintain adequate levels of antioxidants in patients and in the population at risk for ALS. In this population, adequate levels may be in excess of the RDA. Periodic assessment of antioxidant levels is indicated in this population.

Because of the loss of motor function in ALS patients, they usually develop severe dysphagia, and they often become malnourished from inadequate intake.[31] In addition, impaired respiratory function often demands more energy. Therefore, in end stage treatment, supplying sufficient energy to these patients to maximize life quality is the primary goal.

Guam/ALS/Parkinsons/Dementia (GAPD)

GAPD is a very slowly progressing neurotoxicity apparently induced by diet. The disease, once common in the Chamorro natives of the South Pacific, seems to be disappearing.[32] Cycad seeds, which were part of the Chamorron diet and medicine, appear to contain a neurotoxin that exhibits its effects over decades. Indeed, a very similar disease can be produced in monkeys by feeding them the seeds.[33]

Tardive Dyskinesia (TD)

TD is characterized by choreoform movements, particularly of the tongue, lips, and limbs. It is caused by the chronic use of neuroleptic drugs in the treatment of schizophrenia. Neuroleptic activity is generally exhibited through binding to dopamine receptors. That TD is caused by destruction of susceptible dopaminergic neurons has yet to be shown, but the symptoms produced are very similar to those seen in Parkinson's disease. Treatment with L-DOPA is contraindicated in schizophrenics because it is likely to exacerbate the psychosis. Vitamin E has been used to treat TD in schizophrenic patients, but there is disagreement on whether or not it has an effect.[34] Choline (150-200 mg/kg/d) has been

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used successfully as a therapy for TD.[35] Administration of the choline as lecithin will prevent the fishy odor associated with the ingestion of high-dose choline.

Neurodevelopmental Diseases

Neural Tube Defects (NTDs)

NTDs are the result of abnormal fetal development in which the neural tube fails to mature normally. NTDs range widely in severity from a very mild spina bifida that may escape notice until adulthood to anencephaly, a fatal birth defect in which the brain fails to grow in utero. Since NTDs are structural defects, most treatments of nonfatal NTDs involve surgery.

NTDs have many causes including diet, drugs, smoking, and genetic susceptibility. Use of several drugs, including the anticonvulsants discussed above, has been associated with increased incidence of NTDs in babies born to mothers taking these drugs, particularly during the formation and closure of the neural tube (16 to 26 days post fertilization). Drugs that interfere with folate absorption or metabolism are particular risks. Diets limited in folate are also known to increase susceptibility to NTDs. This subject is thoroughly reviewed by Lewis et al.[36]

The Center for Disease Control in the United States requested the Food and Drug Administration to mandate that all flour sold in the U.S. be supplemented with folic acid as a mechanism for preventing NTDs. That supplementation has been implemented; data are expected soon to determine the success of this endeavor in decreasing NTDs. Data on hand indicate that folate intake and folate status have already improved.[37]

Schizophrenia

The inclusion of schizophrenia under neurodevelopmental diseases may be controversial. Schizophrenia is still a catchall for a number of diseases that likely have different etiologies.[38,39] However, genetic and structural studies indicate that both genetic and developmental processes are involved in the disease process.[38] Despite significant effort to identify the genetic correlates of schizophrenia, the search has so far been unsuccessful. Moreover, dysmorphology of neurons in the frontal and temporal lobes of the cortex of schizophrenics[38] and the increased incidence of birth of schizophrenics in the winter/spring (environmental factors[39]), indicate that abnormal development (probably in utero) is involved in the formation of the prepsychotic brain. However, whether schizophrenia, or more appropriately, the schizophrenias are caused by disordered developmental processes remains to be proven. Nevertheless, for now it appears most likely that some (or most) are neurodevelopmentally-caused disorders.

Schizophrenia is most often treated with neuroleptics, which can cause tardive dyskinesia (see above) but also are associated with weight gain in the patients. The weight gain correlates with symptom improvement,[40] an observation that can be interpreted in various ways. Neuroleptics also seem to have a negative effect on plasma indicators of nutritional status,[41] indicating that neuroleptics have effects on nutrient absorption or metabolism that should be evaluated periodically. In another study it was shown that schizophrenics consistently had lower plasma vitamin C levels than other hospitalized controls.[42] Whether this is a drug/nutrient interaction or an increased requirement by schizophrenics for

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vitamin C is unknown, but in either case schizophrenics should be given more vitamin C to attain normal plasma levels.

As in several other neurological disorders, treatment with n-6 and n-3 fatty acids improves symptoms in schizophrenia. Apparently overactivity of phospholipase A_2 causes a vulnerability of these fatty acids to oxidation, resulting in a relative depletion.[43] Dietary replacement ameliorates symptoms by restoring function. Schizophrenics apparently have an increased need for the essential fats, but replacing them, while it improves the symptoms, should not be considered a treatment of the disease, but a nutritional requirement in this population.

Affective Disorders

The primary affective disorders are depression and bipolar disorder. Depression is often divided into endogenous and reactive depression. Reactive depression is a depression of mood in response to an adverse life event. Endogenous depression often has the same symptoms as reactive depression in the absence of any specific adverse life event. Bipolar disorder is characterized by periods of depression interspersed with periods of mania often occurring in a regularly cycling pattern.

The preferred treatment for bipolar disorder is lithium carbonate. Lithium is successful in ameliorating symptoms of both the mania and the depression in most patients with bipolar disorder. It is thought that the mechanism by which this occurs is related to the dampening effect that lithium has on the phosphoinositide cascade.[38]

Lithium is sometimes an effective treatment for unipolar depression as well. However, depression is more commonly treated with tricyclic antidepressants, and more recently with specific serotonin reuptake inhibitors. These drugs are the successors to the monoamine oxidase inhibitors that were used as the first round of effective antidepressants. While monoamine oxidase inhibitors are little used as antidepressants anymore, their use is associated with the potential for toxicity by amines (particularly tyramine) found in some foods.[18] These foods are discussed in the "user friendly MAOI diet" in the section on Parkinson's disease.

Lithium absorption in the gut is inhibited by high salt concentration in the diet,[44] so effective treatment of bipolar disorder is facilitated by a low-salt diet. Care must be taken to balance the dietary salt and the lithium dose, because lithium overdose can cause permanent neurological damage, and the therapeutic window for lithium is relatively narrow.

S-adenosylmethionine, the naturally occurring condensation product of ATP and methionine and the universal methyl donor, has been shown to be an effective antidepressant,[45] just as effective as the tricyclic antidepressants, and with fewer side effects. Indeed, clinical improvement in depressed patients is correlated with plasma levels of S-adenosylmethionine regardless of whether the patients were treated with S-adenosylmethionine or a tricyclic antidepressant.[46] Even though S-adenosylmethionine is a naturally occurring chemical that is found in all foods, it is doubtful that the treatment of depression with S-adenosylmethionine should be considered nutritional therapy, because the doses used (400 mg, tid, PO) are pharmacological. The mechanism by which S-adenosylmethionine improves the symptoms of depression are not yet understood, but it is thought that the methylation process is involved. In support of this hypothesis is the repeated observation that folate deficiency is common in depressed patients and that symptoms improve with folate supplementation whether concomitant with pharmacotherapy or using folate alone.[47] Therefore, it is recommended that folate supplementation be a standard adjunct to pharmacotherapy of depressed patients.

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Depression is also characterized by low levels of n-3 polyunsaturated fatty acids (PUFA) in both erythrocyte membranes and plasma. Rather than being a simple deficiency of n-3 PUFA, the ratio of n-6 PUFA/n-3 PUFA may be a problem in depressed patients.[48] This observation may correlate with the action of lithium on the phosphoinositide cascade. In the phosphoinositide cascade the fatty acid substituted in the two position of the phosphoinositide is often a PUFA. If the cascade is poorly controlled in depression or mania, then a deficiency of n-3 fatty acids or an abnormal ratio of n-6/n-3 might be induced by the lack of control. Since the n-3 fatty acids are much more limited in Western diets, a relative deficiency of the n-3 fatty acid would be expected. An increased intake of n-3 PUFA might then ameliorate the symptoms of depression or bipolar disorder. As with schizophrenia, it may be better to consider the increased need for n-3 PUFA in patients with affective disorder a dietary requirement in this patient population rather than a treatment for the disorder.

Tryptophan appears to be a moderately effective treatment for mild depression but does not seem to be effective against severe depression.[35] Tryptophan does seem to be an effective soporific.[35] Small studies indicate that tryptophan is antimanic, but large controlled studies have not been done.[35] Tyrosine may have antidepressant actions in some cases of "dopamine dependent" depression and it may be anxiolytic in stressful situations. These observations have not been established in a large controlled study, but significant differences have been found in small studies.[35] Finally, another nutrient, lecithin (probably the choline portion), has been credited as a significant treatment for mania,[35] but more data are needed.

Hyperactivity

Attention Deficit Hyperactive Disorder (ADHD), a growing problem in children, is either being more frequently or more efficiently diagnosed or the disorder is increasing in frequency in the population. Feingold[49] was convinced that either the salicylates in foods or food additives (colors or flavors) were responsible for the hyperkinesis in children. However, little evidence has been generated to support this hypothesis, even though foods have been shown to have an effect on hyperkinesis in children.[50] Whether the effect is caused by one of Feingold's food components, a nutrient deficiency or food allergy, or a combination of these factors is still an open question. Because of the difficulty in doing research with children, the difficulty in diagnosing the disorder, and the widespread use of methylphenidate to treat the disorder, good research on the causes of hyperactivity is difficult to find. At this time it is difficult to make any solid recommendations for treatment of hyperactivity with the exception that most children would benefit from a more balanced diet with more fresh fruits and vegetables and less fast-food fare.

Metabolic Diseases

Encephalopathies

Encephalopathies are characterized by a gradual decrease in neurological function as toxicity resulting from failure of the liver to remove toxins from the blood progresses.[51] Initial symptoms include slowed reactions, confusion, and changes in mood. As the toxicity becomes more serious the patient becomes drowsy and his/her behavior deteriorates.

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The third stage, according to the West Haven criteria, is the induction of a stuporous state with marked confusion and slurred speech. This can be followed by a lapse into coma in which the patient is totally unresponsive. Two common types of encephalopathy are the Wernicke-Korsakoff Syndrome and hepatic encephalopathy.

Wernicke-Korsakoff Syndrome (WKS)

WKS results from thiamine deficiency usually secondary to alcoholism, but can result from other diseases as well, e.g., AIDS or gastrointestinal disease leading to poor absorption of thiamine. WKS exhibits a strictly central nervous system (CNS) pathology.[52] Beriberi, which also results from thiamine deficiency but is rarely seen in Western Society, exhibits peripheral neuropathology. Treatment of WKS is a challenge because it is difficult to recognize the disease in time to prevent permanent damage. However, early treatment will arrest the progress of the disease.[52]

The Wernicke phase of the disease is an acute phase characterized by staggering gait and paralysis of eye movements, and is reversible by thiamine therapy (50 mg/d for 3 days, iv). The chronic Korsakoff phase, a debilitating loss of working memory, is generally not reversible by thiamine.[53]

Hepatic Encephalopathy

Hepatic encephalopathies have a variety of causes that result in failure by the liver to remove toxins from the blood, causing a depression of CNS function. The biochemical mechanism that causes the decreased speed of neurological function is unknown, but most encephalopathies are characterized by increased plasma ammonia concentrations. Traditionally, these encephalopathies have been treated by partial or complete dietary protein withdrawal. This is no longer recommended. Vegetable protein is tolerated better by these patients than is animal protein because of the higher branched chain amino acid component of vegetable protein, and plasma levels of branched chain amino acids are generally lower in patients with hepatic encephalopathy. Non-absorbable disaccharides (lactulose or lactitol) are often used because they inhibit the uptake of toxins sometimes produced by enteric flora and they may alter the absorption of ammonia produced in the gut by the enteric flora.[51,54] The decreased uptake of ammonia in the presence of disaccharides is probably due to acidification of the gut by the metabolism of these disaccharides to organic acids by the gut flora.

Neuropathies

Neuropathies are characterized by the failure of the peripheral nervous system (PNS). Neuropathies may result from a slowed conduction in the PNS, from the absence of sensory input or motor output through specific peripheral nerves, or from diseases leading to the degeneration of specific peripheral nerves. Neuropathies are related to the encephalopathies in that they are generally caused by toxins acting on the peripheral nervous system. These toxins may be caused by genetic defects that allow the accumulation of toxins, by ingestion of toxic substances, or by failure of the body's metabolic control to limit the amounts of potentially toxic metabolites. Genetic neuropathies are discussed under Inborn Errors below. In this section only those neuropathies that have a nutritional component, either cause or treatment, are listed.

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Pyridoxine Toxicity

Pyridoxine toxicity generally results from self medication with large doses of vitamin B_6.[55] Pyridoxine binds to proteins in the endoneurium of the PNS axons and blocks normal neuronal function, yielding a sensory polyneuropathy. Ironically, pyridoxine deficiency also contributes to the polyneuropathy of B-complex deficiency.[56] Treatment depends on the cause. Toxicity is treated with cessation of the megadoses of vitamin B_6, and B-complex deficiency is treated with supplements of the B vitamins.

Diabetic Neuropathy

Diabetic neuropathy normally presents as a slowly progressing, mixed sensorimotor, autonomic polyneuropathy. It is probably secondary to diabetes-induced vascular disease. As with other diabetic-induced medical problems, the best treatment is prevention by maintaining control of plasma glucose levels.[57]

Vitamin B_{12} Deficiency

B_{12} deficiency can result in combined system disease characterized by parasthesias, spastic weakness, and malaise. Often these neurological abnormalities are irreversible by the time symptoms are obvious.[56] Vitamin B_{12} deficiency also causes megaloblastic anemia which, in the past, was used as a signal to check plasma B_{12} levels. However, the recent decision to supplement flour with folic acid to prevent birth defects may mask vitamin B_{12} deficiency possibly until the neurological damage is irreversible. Greater care must now be taken to monitor plasma vitamin B_{12} states, especially in vegans. The safest treatment for suspected vitamin B_{12} deficiency is injection of 5 to 15 μg hydroxycobalamin, im. However, injections are expensive, and high dose vitamin B_{12} (150 to 500 μg/d, po) is usually adequate even in cases of pernicious anemia (absence of intrinsic factor).[58] However, to be safe in cases of pernicious anemia, monthly injections of vitamin B_{12} (50 to 150 μg) may be necessary. In the absence of pernicious anemia it is recommended that patients receive 5 to 25 μg/d, po after their plasma levels have been increased to normal range by injection or by the high dose regimen.

Pantothenic Acid Deficiency

Pantothenic acid deficiency leads to parasthesias involving demyelination of peripheral nerves.[56] Pantothenate is a component of coenzyme A which is essential in the synthesis of acetylcholine, the generation of energy in the Krebs cycle, and the synthesis of a number of other metabolic intermediates. Its involvement in the synthesis of fats is probably responsible for the demyelinating effect of its deficiency. Because pantothenic acid is so widely available in the diet, its deficiency normally occurs only in the context of B-complex deficiency. Pantothenic acid deficiency is therefore treated with the daily ingestion of a B-complex vitamin containing at least 10 mg of pantothenic acid.[59]

Inborn Errors (Genetic Diseases)

Peroxisomal Diseases

Peroxisomal diseases are characterized by dysmyelination, hypotonia, retardation, and visual and auditory effects. Peroxisomes are responsible for the oxidative catabolism of a

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myriad of metabolic products which, if allowed to accumulate, might be toxic to cellular processes. Peroxisomal diseases are a result of either the failure of peroxisome biogenesis in the patient or a defect in one of the proteins essential to the normal function of peroxisomes. Significant advances have been made recently in understanding the genetic causes of these disorders.[60,61] Sixteen separable disorders have been identified, 12 of which cause severe neurological damage.[62] Two groups of these disorders are addressed here.

Adrenoleukodystrophy (ALD) and Adrenomyeloneuropathy (AMN)

ALD and AMN are X-linked genetic disorders characterized by the accumulation of very long chain fatty acids (24:0 and 26:0). The same genetic defect has been identified in both phenotypes. The mutant protein is a peroxisome membrane protein involved in the transport of very long chain fatty acids into the peroxisome for degradation. By a mechanism not yet understood, this deficiency leads to demyelination and progressive loss of neural function. The accumulation of very long chain fatty acids also affects the function of the adrenal gland, and ALD and AMN patients often suffer from primary adrenal insufficiency prior to the onset of neurological symptoms. Dietary restriction of very long chain fatty acids and dietary administration of Lorenzo's oil (glyceryltrioleate + glyceryltrierucate) lower the plasma levels of the primary very long chain fatty acids, but once neurological symptoms have appeared, this treatment does little to reverse the progress of the disease.[63] However, it appears to slow the progress of the disease if it is administered prior to the onset of neurological symptoms.[63] This treatment apparently causes a deficiency of the essential polyunsaturated fatty acids so that supplementation with docosahexaenoic acid and arachadonic acid may be necessary.[64] The treatment of choice at this time is a bone marrow transplant if a suitable donor can be found.

Refsum's Disease — Zellweger's Syndrome

Refsum's disease, Zellweger's syndrome, and neonatal adrenoleukodystrophy are all part of a continuum of diseases that are genetically related.[60,65] They are autosomal recessive defects in the assembly of the peroxisomal system for the oxidation of unusual fatty acids. The inability to catabolize branched chain or very long chain fatty acids leads to the incorporation of the accumulated metabolites into myelin, which then does not function normally. Decreasing the amount of the unusual fats (e.g., phytanic acid or 24:0 and 26:0) in the diet improves the polyneuropathy.[57] Phytanic acid is found in animal fat, especially dairy products. Diets low in animal fat and dairy products relieve some of the symptoms. These peroxisomal disorders can also be treated with Lorenzo's oil, and, as with the ALD and AMN, the plasma levels of n-6 and n-3 polyunsaturated fatty acids should be monitored and supplemented as necessary.[64] Arachidonic and docosahexaenoic acids are the primary representatives of the n-6 and n-3 fatty acids, respectively, in the plasma. Because arachidonic acid is widely available in the diet, the n-3 fatty acids are the most likely to be deficient. The n-3 fatty acids are present in fish oils or in fish, and supplements of both arachidonic acid (n-6) and either docosahexaenoic or eicosapentaenoic acids (n-3) are available as dietary supplements.

Maple Syrup Urine Diseases

There are as many forms of maple syrup urine disease as there are enzymes that catabolize the branched chain amino acids. The disorders present as acidemias or acidurias. Accumulation of many of the metabolites of the branched chain amino acids is toxic. Symptoms commonly include vomiting, lethargy, metabolic acidosis, ketonuria, seizures, mental

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retardation, and coma. The symptoms typically present during the first few months of life, but milder forms of the genetic defects may not appear until the fourth or fifth year. There are forms of maple syrup urine disease that are responsive to thiamine. These are genetic variants of the branched chain dehydrogenase complex that do not bind thiamine as tightly as the wild type.[56] Some forms of maple syrup urine disease are also responsive to diets restricted in branched chain amino acids. However, the only way to insure adequate intake of the essential amino acids while restricting the branched chain amino acids is to feed the patient a defined amino acid diet.[66] There are several known enzyme defects in the processing of the organic acids formed in the catabolism of the branched chain amino acids. Most of these benefit from a restricted protein diet and some from high dose biotin (10 to 40 mg/d).[66] Those suffering from methylmalonic acidemia may also benefit from high dose (1 to 2 mg/d) vitamin B_{12} therapy.[66]

Functional Biotin Deficiency

Biotin is involved in the carboxylation of organic acids. It is essential for the initiation of gluconeogenesis (carboxylation of pyruvate), the initiation of fatty acid synthesis (carboxylation of acetylCoA), the catabolism of leucine (carboxylation of methylcrotonyl CoA), and the catabolism of propionate from odd chain fatty acids and several amino acids (carboxylation of propionylCoA). Biotin is attached covalently to each of these carboxylases by holocarboxylase synthetase. It is conserved when the carboxylase is degraded by the enzyme biotinidase, which cleaves the covalent attachment. Deficiency of either of these enzymes can cause neurological problems. Both deficiencies are characterized by high plasma levels of organic acids, but the effects of the holocarboxylase synthetase deficiency are more serious and more immediate, because it causes a decreased blood pH. Untreated, the deficiencies will result in psychomotor retardation, seizures, cerebellar signs, and peripheral symptoms at three to six months for biotinidase deficiency, and earlier for holocarboxylase synthetase deficiency. Prompt treatment with pharmacological doses of biotin (10 to 40 mg/d, orally) improves outcome considerably.[66]

Glucose Transporter Deficiency

The brain uses glucose almost exclusively as an energy source. The transport of glucose into the brain by facilitated diffusion is normally not rate-limiting to energy use. However, a relatively newly identified defect in the glucose transporter causes a limited energy supply to the brain.[67] The incidence of this defect in the population is not yet known, but it is suspected that some cases of cerebral palsy and sudden infant death syndrome may be caused by this defect. Symptoms include infantile seizures and developmental delay. It can be diagnosed by hypoglycorrhachia and low to low normal cerebrospinal fluid lactate levels. It can be treated effectively using the ketogenic diet (Tables 67.3 through 67.8). Ketone bodies provide an alternate energy source to the brain, but are not present in significant quantities in the blood unless induced by a high fat, low carbohydrate, low protein diet.

Glycogen Storage Diseases

Fructose-1,6-biphosphatase deficiency, glucose-6-phosphatase deficiency, or deficiency of the glucose-6-phosphate translocation system causes the lack of glucose availability between meals and leads to hepatomegaly, bleeding diathesis, neutropenia, and neuro-

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logical symptoms from the hypoglycemia. Treatment consists of frequent small meals which may include nocturnal intragastric feeding.[68]

Deficiencies of Fatty Acid Beta-Oxidation

There are several enzymes involved in the oxidation of fatty acids as a source of energy. Carnitine is also needed to transport the fatty acids into the mitochondrion for oxidation. Defects in these processes can cause neurological symptoms including drowsiness, stupor, and coma during acute metabolic crises probably caused by diet-induced hypoglycemia accompanied by a hypoketonemia due to the lack of fatty acid oxidation. The hypoketonemia prevents the brain from receiving the energy it needs to function in the absence of glucose. The treatment is to avoid hypoglycemic states where fatty acids would need to be used for energy.[68] Glycogen is available for immediate energy needs, so that hypoglycemia does not develop as quickly as in glycogen storage diseases. Prolonged fasting or extended exercise, however, deplete the glycogen stores and lead to neurological symptoms and potential neurological damage.

Pyruvate Dehydrogenase Deficiency

As expected from its central position in intermediary metabolism, pyruvate dehydrogenase deficiency is complex. Symptoms range from a mild encephalopathy with retardation to death.[68] It is sex-linked so that males are more often affected. Depending on the defect, the problem may be treatable, especially when it appears in females. Treatment with thiamine, lipoic acid, or ketogenic diets is sometimes partially successful.[68] Treatment with thiamine (25 to 100 mg, po) or lipoic acid (5 to 10 mg, po) requires a partially functional enzyme that responds to pharmacological doses of these vitamins. The use of a ketogenic diet (see Tables 67.3 through 67.8) is an attempt to bypass energy production from carbohydrates, a process which is completely dependent on the activity of pyruvate dehydrogenase.

Defects in the Respiratory Chain Proteins

Abnormalities in the mitochondrial respiratory chain are characterized by both muscle and central nervous system symptoms. Central symptoms include ataxia, pyramidal signs, and dementia, but the course is varied, attributable to the number of proteins involved and the potential for considerable differences in vulnerability. Since the respiratory chain is a process of electron transfer, some redox vitamins can substitute, although very inefficiently, for the abnormal proteins. Vitamin C and vitamin K have been used successfully in this way.[68] Doses differ between patients, but because neither vitamin C nor vitamin K_1 exhibit significant toxicity when taken orally, the doses of both vitamins can be titrated to each patient.

Phenylketonuria (PKU)

There are many genetic forms of PKU. Usually the defect is in the gene for the enzyme phenylalanine hydroxylase. Some of these defects cause a complete loss of enzyme activity, while others cause only partial losses. Because of this variation in activity, some patients are more tolerant to phenylalanine in their diets than are others. The neurological effects

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of this disease — mental retardation and progressive motor dysfunction — are apparently due to the high blood phenylalanine levels and not to the high plasma levels of phenylalanine metabolites.[66] It is essential that the defect be identified early and treated as soon as possible. PKU at any age is treated using a diet that decreases the amount of phenylalanine ingested. Phenylalanine is so common in high protein foods that it is impossible to ingest sufficient protein to satisfy other amino acid requirements and still maintain the plasma concentration of phenylalanine between 120 and 360 μM in patients with little or no phenylalanine hydroxylase activity. Therefore, high protein foods (see Table 67.9) are usually completely restricted, and a casein hydrolysate stripped of phenylalanine is substituted. Because high protein foods are generally responsible for a significant portion of the vitamins and minerals in the diet, the hydrolysate is usually fortified with vitamins and minerals to ensure that the patients using the hydrolysate as a primary amino acid source do not become deficient in vitamins and minerals. There are several commercial sources of the fortified hydrolysate. It is advisable, particularly in PKU patients with no hydroxylase activity, to continue treatment of the disease with the fortified hydrolysate through the teen years and at least into adulthood.[69,70] Monitoring phenylalanine levels in the plasma is the measure of success in treating the disease. Plasma phenylalanine levels should be maintained between 120 and 360 μM. Because of the expense of the fortified hydrolysate, attempts have been made to restrict dietary phenylalanine without the aid of the fortified hydrolysate. This is difficult at best, often resulting in either a deficiency of essential amino acid intake, a deficiency in one or more of the vitamins, or a deficit in energy intake. Each of these has serious consequences to the patient. Early detection and successful treatment of PKU can lead to a normal independent life.

Phenylketonuria can also be caused by a defect in the metabolism of biopterin, a cofactor in the hydroxylation of phenylalanine. This defect cannot be treated solely by restricting phenylalanine, because it causes a lack of hydroxylation of tyrosine and tryptophan as well. The hydroxylated products of tyrosine and tryptophan are precursors of the neurotransmitters dopamine and serotonin, and consequently, lack of these hydroxylations also has neurological effects. The prognosis for a defect in biopterin metabolism is not as positive as that for a defect in phenylalanine hydroxylase.

Homocystinuria

Homocystinuria can be the result of any one of a series of genetic defects in the transsulfuration pathway. These defects can be either in the enzymes of transsulfuration or in the metabolism of the vitamins that act as cofactors in the pathway. Symptoms are variable but usually include mental retardation, and often include psychiatric disorders, and sometimes seizures. Vascular damage is evident in those who survive into the third decade. Treatment is sometimes successful. High-dose vitamin B_6 (250 to 500 mg/d) works in some cases of cystathionine-beta-synthetase deficiency, depending on the effect of the genetic defect on the capacity of the enzyme to bind B_6. Betaine (6 to 12 g/d) usually helps to remethylate the homocysteine. Defects in the metabolism of folate can also be treated with betaine, while defects in the metabolism of vitamin B_{12} are generally best treated with injections of hydroxycobalamin.[66]

Urea Cycle Defects

There are several enzymes or transporters that can cause the typical hyperammonemia of urea cycle defects. In addition to hyperammonemia, these defects are generally characterized by high serum concentrations of one of the urea cycle intermediates. Glutamine and

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alanine are usually high, and arginine is low. Orotic acid is often high, especially in ornithine transcarbamylase deficiency, but is normal or low in carbamylphosphate synthetase deficiency. Urea cycle defects are often fatal in the neonatal period, so therapy should start immediately. Patients can be maintained on a low protein diet with adjunct therapy with sodium benzoate (250 mg/kg/d) and phenyl acetate (250 mg/kg/d).[71] These aromatics react with glycine and glutamine, respectively, and are excreted as conjugates of these amino acids, thus excreting ammonia in an alternate form. Arginine can be used as an adjunct to treatment in citrullinemia and arginosuccinic acidemia because it can stimulate the excretion of ammonia as citrulline and arginosuccinate. Arginine is given as a dietary supplement in sufficient quantities to yield a normal plasma level of arginine. The amount of the arginine supplement will depend on the genetic defect, but starting with 700 mg/kg/d is recommended with subsequent titration to normal plasma levels.[71] Lysinuric protein intolerance, a failure of the proximal tubule to reabsorb the dibasic amino acids lysine and ornithine, can be treated by oral citrulline, which is reabsorbed and can act as a source of ornithine for the mitochondrial initiation of the urea cycle.[66] Citrulline is given as a dietary supplement at a rate that allows the plasma ornithine to be normalized.

Glutamate Decarboxylase Deficiency

Glutamate decarboxylase is the enzyme responsible for the synthesis of gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter. Defective glutamate decarboxylase activity causes a severe seizure disorder, which may begin in utero. Depending on the specific genetic defect, the enzyme can sometimes be stimulated by high dose pyridoxine (10 to 100 mg/d) given parenterally.[66]

Wilson's Disease (WD) or Hepatolenticular Degeneration

WD is caused by copper toxicosis. Copper concentrations in the plasma are normally controlled by an enterohepatic mechanism that causes the excretion of excess copper in the stool. The genetic defect causing WD has been localized to chromosome 13. The defective protein is not ceruloplasmin, since the gene for ceruloplasmin has been localized to chromosome 3. Dietary restriction of copper may delay the onset of symptoms, but it is not preventive. The toxicity of the copper appears to be induced oxidation that damages tissues, particularly nervous tissue, leading to a myriad of symptoms including tremors, rigidity, dysarthria, dysphagia, and psychiatric disorders. The preferred treatment of Wilson's disease is penicillamine (1 g/d, at least 30 min before or 2 hr after meals), a chelator that binds copper and is excreted by the kidney. Trientine at the same dose also works in the same way for patients who have reactions to penicillamine. Zinc supplements (150 mg/d, before meals) can replace copper and are sometimes used, but care must be taken not to give zinc and either of the chelators at the same time, because they can neutralize each other.[72]

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